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<b>(21) International Application Number:</b> PCT/SE98/01066 <b>(22) International Filing Date:</b> 4 June 1998 (04.06.98) <b>(30) Priority Data:</b> 9702305-5 17 June 1997 (17.06.97) SE <b>(71) Applicant (for all designated States except US):</b> ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> ANDERSSON, Kjell [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). BOLJE, Maria [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). LINDSTEDT, Eva-Lotte [SE/SE]; Astra Hässle AB, S-431 81 Mölndal (SE). LJUNG, Bengt [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). NORDÉN, Bo [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). <b>(74) Agent:</b> ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).	<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>	
<b>(54) Title:</b> NEW THIAZOLIDINEDIONE, OXAZOLIDINEDIONE AND OXADIAZOLIDINEDIONE DERIVATIVES  <b>(57) Abstract</b>  Novel thiazolidinedione, oxazolidinedione and oxadiazolidinedione derivatives, process for their manufacture, pharmaceutical preparations containing them and the use of the compounds in conditions associated with insulin resistance.		

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## NEW THIAZOLIDINEDIONE, OXAZOLIDINEDIONE AND OXADIAZOLIDINEDIONE DERIVATIVES

### Field of invention

The present invention relates to certain novel thiazolidinedione, oxazolidinedione and oxadiazolidinedione derivatives, to a process for preparing such derivatives, having the utility in clinical conditions associated with insulin resistance, to methods for their therapeutic use and to pharmaceutical compositions containing them.

### Background of the invention

Insulin resistance, defined as reduced sensitivity to the actions of insulin in the whole body or individual tissues such as skeletal muscle, myocardium, fat and liver prevail in many individuals with and without diabetes mellitus. The insulin resistance syndrome, IRS, refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinemia, possibly non insulin dependent diabetes mellitus (NIDDM); arterial hypertension; central (visceral) obesity; dyslipidemia observed as deranged lipoprotein levels typically characterized by elevated VLDL (very low density lipoproteins) and reduced HDL (high density lipoproteins) concentrations; and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In non-insulin dependent diabetes mellitus these atherosclerosis related conditions cause up to 80% of all deaths.

In clinical medicine there is at present only limited awareness of the need to increase the insulin sensitivity in IRS and thus to correct the dyslipidemia which is considered to cause the accelerated progress of atherosclerosis.

Furthermore there is at present no pharmacotherapy available to adequately correct the metabolic derangements associated with IRS. To date, the treatment of NIDDM has been focused on correction of the deranged control of carbohydrate metabolism associated with the disease. Stimulation of endogenous insulin secretion by means of secretagogues, like  
5 sulphonylureas, and if necessary administration of exogenous insulin are methods frequently used to normalize blood sugar but that will, if anything, further enhance insulin resistance and will not correct the other manifestations of IRS nor reduce cardiovascular morbidity and mortality. In addition such treatment involves a significant risk of hypoglycemia with associated complications.

10

Other therapeutic strategies have focused on aberrations in glucose metabolism or absorption, including biguanides, such as methformin, or glucosidase inhibitors, such as acarbose. Although these agents have been efficacious to a degree, their limited clinical effect is associated with side effects.

15

A novel therapeutic strategy involves the use of insulin sensitizing agents, such as the thiazolidinediones. Ciglitazone is the prototype in this class. In IRS these compounds seem to correct insulin resistance and the associated hypertriglyceridaemia and hyperinsulinemia, as well as hyperglycemia in diabetes, by improving insulin sensitivity  
20 via an effect on lipid transport and handling, leading to enhanced insulin action in skeletal muscle, liver and adipose tissue.

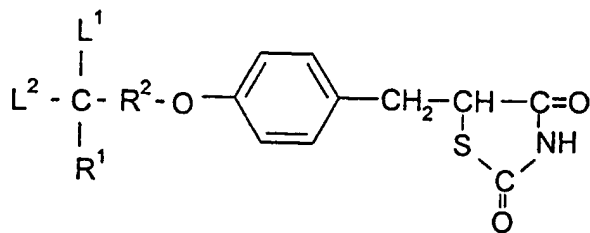
Ciglitazone as well as later described thiazolidinediones in clinical development either has been discontinued reportedly due to unacceptable toxicity or show inadequate potency.  
25 Therefore there is a need for new and better compounds with insulin sensitizing properties.

#### Prior art

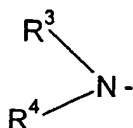
EP 08 203 discloses thiazolidinedione derivatives of the general formula:

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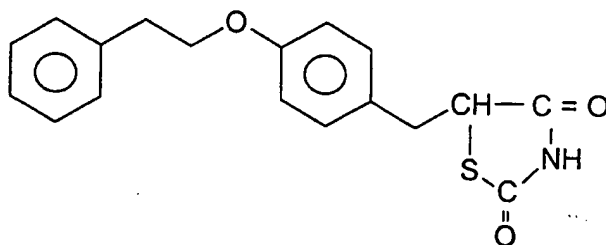
wherein  $R^1$  is alkyl, cycloalkyl, phenylalkyl, phenyl, a five- or six membered heterocyclic group including one or two hetero-atoms selected from nitrogen, oxygen and sulphur or a  
 5 group of the formula



(where  $R^3$  and  $R^4$  are the same or different and each is lower alkyl or  $R^3$  and  $R^4$  are  
 10 combined with each other either directly or interrupted by a heteroatom selected from nitrogen, oxygen and sulphur to form a five- or six-membered ring);  $R^2$  means a bond or a lower alkylene group;  $L^1$  and  $L^2$  are the same or different and each is lower alkyl or  $L^1$  and  $L^2$  are combined to form an alkylene group, provided that, when  $R^1$  is other than alkyl,  $L^1$  and  $L^2$  may be further hydrogen, as remedies for diabetes and hyperlipemia.

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One compound comprised by the formula above is

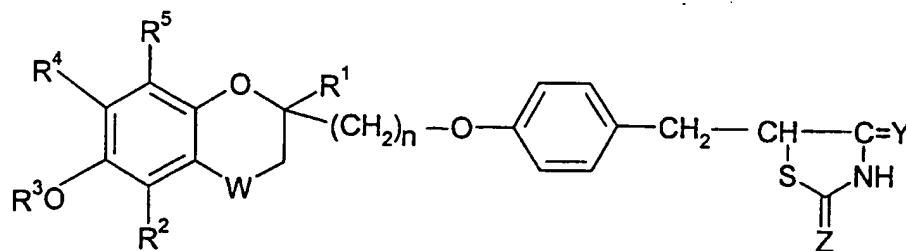


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This compound has been reported [Chem. Pharm. Bull. 30(10)3580-3600 (1982)] to have undesirable effects, such as a considerable increase in liver lipids.

EP 139 421 discloses a compound of the formula

10



wherein

$R^1$  and  $R^2$  are the same or different and each represents a hydrogen atom or a  $C_1$ - $C_5$  alkyl

15

group;  
 $R^3$  represents a hydrogen atom, a  $C_1$ - $C_6$  aliphatic acyl group, a ( $C_5$ - $C_7$  cycloalkane) carbonyl group, an aromatic acyl group which is a benzoyl or naphthoyl group optionally with one or more nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents, a heterocyclic acyl group having one or more oxygen, sulphur or nitrogen  
 20 hetero atoms and with 4 to 7 ring atoms, an optionally halosubstituted phenylacetyl or phenylpropionyl group, a cinnamoyl group, a ( $C_1$ - $C_6$  alkoxy) carbonyl group or a benzyloxycarbonyl group;

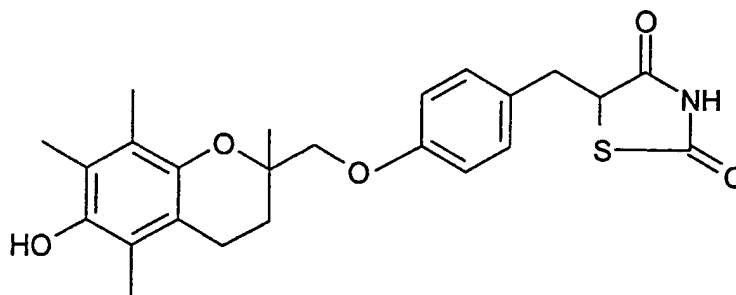
$R^4$  and  $R^5$  are the same or different and each represents a hydrogen atom, a  $C_1$ - $C_5$  alkyl group or a  $C_1$ - $C_5$  alkoxy group, or  $R^4$  and  $R^5$  together represent a  $C_1$ - $C_4$  alkylendioxy group;

$n$  is 1, 2 or 3;

- 5 W represents the  $-CH-$ ,  $>CO$  or  $>CH-OR^6$  group (in which  $R^6$  represents any one of the atoms or groups defined for  $R^3$  and may be the same as or different from  $R^3$ ); and

Y and Z are the same or different and each represents an oxygen atom or an imino ( $=NH$ ) group, having the ability to lower blood lipid and blood sugar levels.

- 10 Among the compounds comprised by the general formula above is troglitazone having the chemical formula

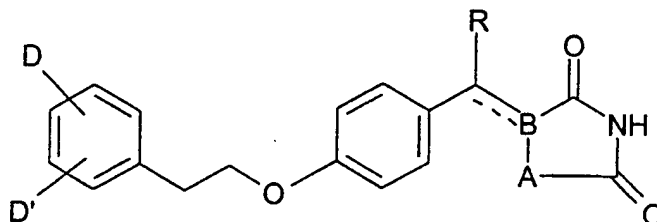


15

This substance has a very low potency in animal models of IRS.

### Description of the invention

- 20 It has now been found that compounds of the general formula (I)



and stereo and optical isomers and racemates thereof as well as pharmaceutically acceptable salts, solvates and hydrates thereof, in which formula

5      $\equiv$  is a single or double bond,

R is H or alkyl,

A is S, O or NH,

B is C, CH or N,

D is situated in the orto, meta or para position and is representing CN or -X-Y-Z,

10     D' is situated in the orto, meta or para position and is representing H, -O-alkyl, alkyl, halogen or -X-Y-Z, wherein

X is O, NR<sup>1</sup>, SO<sub>2</sub> or S and R<sup>1</sup> is H or alkyl,

Y is SO<sub>2</sub>, CO, or a chemical bond,

Z is alkyl, alkyl substituted by one or more fluoro or chloro atoms, aryl, substituted aryl,

15     alkylaryl, OR<sup>2</sup> or NHR<sup>3</sup>, wherein

R<sup>2</sup> is alkyl, aryl, alkylaryl, substituted aryl or substituted alkyl,

R<sup>3</sup> is H, alkyl, aryl, alkylaryl, substituted aryl or substituted alkyl

provided that

when X is O or NR<sup>1</sup>, then Y is either SO<sub>2</sub> or CO and Z is, when Y is a) SO<sub>2</sub>, selected  
 20     from the group consisting of alkyl, alkyl substituted by one or more fluoro or chloro atoms, aryl, substituted aryl and alkylaryl, when Y is b) CO, selected from the group consisting of OR<sup>2</sup> and NHR<sup>3</sup> wherein R<sup>2</sup> and R<sup>3</sup> are as defined above,

when X is SO<sub>2</sub>, then Y is a chemical bond and Z is selected from the group consisting of  
 25     alkyl, alkyl substituted by one or more fluoro or chloro atoms, aryl, substituted aryl, alkylaryl and OR<sup>2</sup>, wherein R<sup>2</sup> is as defined above,



- when X is S, then Y is a chemical bond and Z is selected from the group consisting of alkyl, alkyl substituted by one or more fluor or chloro atoms, aryl, substituted aryl and alkylaryl,
- and further provided that when B is N, A is O,
- 5 are effective in conditions associated with insulin resistance.

Preferred compounds of the invention are those of the formula I wherein

==== is a single or double bond,

R is a H or alkyl,

10 A is S or O,

B is C, CH or N,

D is situated in the orto, meta or para position and is representing -X - Y - Z,

D' is situated in the orto, meta or para position and is representing H, -O-alkyl or -X-Y-Z,

X is O, NR<sup>1</sup>, SO<sub>2</sub> or S wherein R<sup>1</sup> is H or alkyl,

15 Y is SO<sub>2</sub>, CO or a chemical bond,

Z is alkyl, aryl, alkylaryl, substituted aryl, CF<sub>3</sub>, OR<sup>2</sup>, NHR<sup>3</sup>, wherein R<sup>2</sup> and R<sup>3</sup>, are as defined above,

provided that

when X is O or NR<sup>1</sup>, then Y is either SO<sub>2</sub> or CO and Z is, when Y is a) SO<sub>2</sub>, selected  
20 from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl and alkylaryl, when  
Y is b) CO, selected from the group consisting of OR<sup>2</sup> and NHR<sup>3</sup> wherein R<sup>2</sup> and  
R<sup>3</sup> are as defined above,

when X is SO<sub>2</sub>, then Y is a chemical bond and Z is selected from the group consisting of  
alkyl, CF<sub>3</sub>, aryl, substituted aryl, alkylaryl and OR<sup>2</sup>, wherein R<sup>2</sup> is as defined  
25 above,

when X is S, then Y is a chemical bond and Z is selected from the group consisting of  
alkyl, CF<sub>3</sub>, substituted aryl and alkylaryl,

and further provided that when B is N, A is O,

Further preferred compounds of the invention are those of the formula I wherein

==== is a single or double bond,

R is H,

5 A is S,

B is C or CH,

D is situated in the orto, meta or para position and is representing - X - Y - Z,

D' is H,

X is O, NR<sup>1</sup>, SO<sub>2</sub> or S wherein R<sup>1</sup> is H or alkyl,

10 Y is SO<sub>2</sub>, CO or a chemical bond,

Z is alkyl, aryl, alkylaryl, substituted aryl, CF<sub>3</sub>, OR<sup>2</sup> or NHR<sup>3</sup>, wherein R<sup>2</sup> and R<sup>3</sup> are as defined above,

provided that

when X is O or NR<sup>1</sup>, then Y is either SO<sub>2</sub> or CO and Z is, when Y is a) SO<sub>2</sub>, selected  
15 from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl and alkylaryl, when  
Y is b) CO, selected from the group consisting of OR<sup>2</sup> and NHR<sup>3</sup> wherein R<sup>2</sup> and  
R<sup>3</sup> are as defined above,

when X is SO<sub>2</sub>, then Y is a chemical bond and Z is selected from the group consisting of  
alkyl, CF<sub>3</sub>, aryl, substituted aryl, alkylaryl and OR<sup>2</sup>, wherein R<sup>2</sup> is as defined  
20 above,

when X is S, then Y is a chemical bond and Z is selected from the group consisting of  
alkyl, CF<sub>3</sub>, aryl, substituted aryl and alkylaryl.

Still further preferred compounds of the invention are those of the formula I wherein

25 ==== is a single or double bond,

R is H,

A is S,

B is C or CH,

D is situated in the orto, meta or para position and is representing - X - Y - Z,

D' is H,

X is O, NH, SO<sub>2</sub> or S,

Y is SO<sub>2</sub>, CO or a chemical bond,

Z is alkyl, aryl, alkylaryl, substituted aryl, CF<sub>3</sub>, OR<sup>2</sup> or NHR<sup>3</sup>, wherein R<sup>2</sup> and R<sup>3</sup> are as

5 defined above,

provided that

when X is O or NR<sup>1</sup>, then Y is either SO<sub>2</sub> or CO and Z is, when Y is a) SO<sub>2</sub>, selected from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl and alkylaryl, when Y is b) CO, selected from the group consisting of OR<sup>2</sup> and NHR<sup>3</sup> wherein R<sup>2</sup> and R<sup>3</sup> are as defined above,

10

when X is SO<sub>2</sub>, then Y is a chemical bond and Z is selected from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl, alkylaryl and OR<sup>2</sup>, wherein R<sup>2</sup> is as defined above,

when X is S, then Y is a chemical bond and Z is selected from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl and alkylaryl.

15

Still further preferred compounds of the invention are those in the formula I wherein D is situated in the para position.

20 Still further preferred compounds of the invention are those of the formula I wherein

==== is a single bond,

R is H,

A is S,

B is CH,

25 D is situated in the para position and is representing - X - Y - Z,

D' is H,

X is O or NH

Y is SO<sub>2</sub> or CO,

Z is alkyl, aryl alkylaryl, substituted aryl,  $\text{CF}_3$ ,  $\text{OR}^2$  and  $\text{NHR}^3$ , wherein  $\text{R}^2$  and  $\text{R}^3$ , are as defined above,

provided that

when X is O or  $\text{NR}^1$ , then Y is either  $\text{SO}_2$  or CO and Z is, when Y is a)  $\text{SO}_2$ , selected  
 5 from the group consisting of alkyl,  $\text{CF}_3$ , aryl, substituted aryl and alkylaryl, when  
 Y is b) CO, selected from the group consisting of  $\text{OR}^2$  and  $\text{NHR}^3$  wherein  $\text{R}^2$  and  
 $\text{R}^3$  are as defined above.

Still further preferred compounds of the invention are those of the formula I wherein

10  $\text{=====}$  is a single bond,

R is H,

A is S,

B is CH,

D is situated in the para position and is representing - X - Y - Z,

15 D' is H,

X is O or NH

Y is  $\text{SO}_2$  or CO,

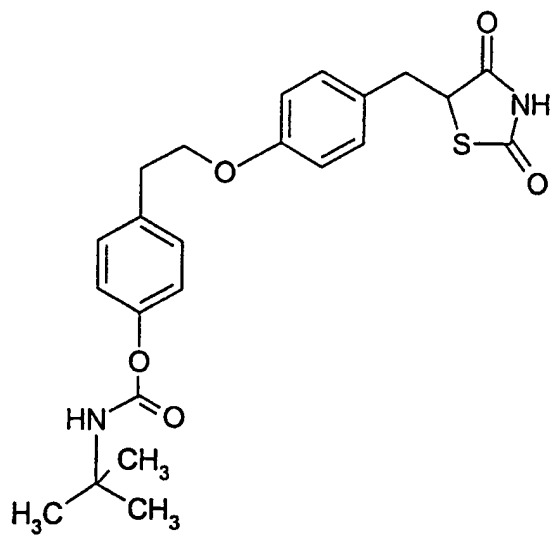
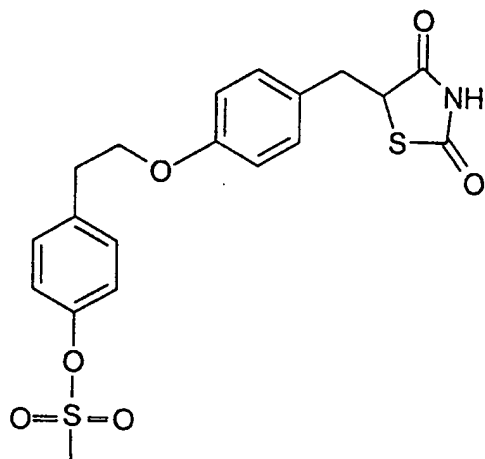
Z is alkyl,  $\text{NHR}^3$  or  $\text{OR}^2$ , wherein  $\text{R}^2$  is alkyl and  $\text{R}^3$  is alkyl,

provided that

20 when X is O or  $\text{NR}^1$ , then Y is either  $\text{SO}_2$  or CO and Z is, when Y is a)  $\text{SO}_2$ , selected  
 from the group consisting of alkyl, when Y is b) CO, selected from the group  
 consisting of  $\text{OR}^2$  and  $\text{NHR}^3$  wherein  $\text{R}^2$  and  $\text{R}^3$  are as defined above.

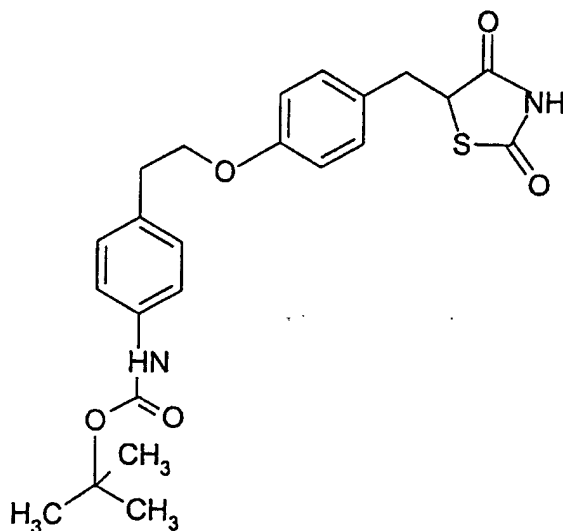
Still further preferred compounds of the invention are those having the chemical formulas

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or



In the present specification the expression "pharmaceutically acceptable salts" is intended to define but is not limited to such base salts as the alkali metal salts (e.g. sodium, lithium and potassium), alkaline earth metal salts (e.g. calcium, barium and magnesium), aluminium, zinc and bismuth salts, ammonium salts, salts with basic amino acids, such as arginine, lysine, and salts with organic amines such as ethanolamine, ethylenediamine, triethanoleamine, benzylphenethylamine, diethylamine, tromethamine, benzathine, chlorprocaine, choline, meglumine, procaine, clemizole and piperazine.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "alkyl" denotes a straight or branched alkyl group having from 1 to 6 atoms. Examples of said alkyl include methyl, ethyl, n-propyl,

isopropyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

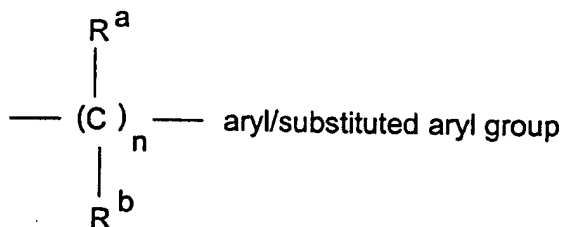
Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine,  
5 bromine or iodine.

Unless otherwise stated or indicated, the term "aryl" denotes a phenyl, furyl, thienyl or pyridyl group.

10 Unless otherwise stated or indicated, the term "substituted aryl" denotes an aryl group as defined above which is substituted by one or more alkyl, alkoxy, halogen, amino or nitro groups.

Unless otherwise stated or indicated, the term "substituted alkyl" denotes an alkyl group as  
15 defined above which is substituted by one or more alkyl, alkoxy, halogen, amino or nitro groups.

Unless otherwise stated or indicated, the term "alkylaryl" denotes a



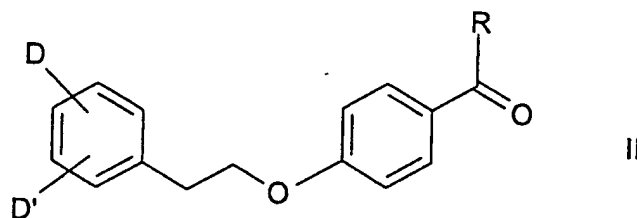
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wherein n is an integer 1 to 6 and  $R^a$  and  $R^b$  are the same or different and each represents a substituted or unsubstituted alkyl or aryl group as defined above.

Methods of preparation

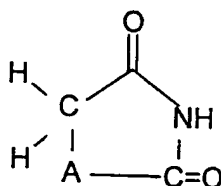
The compounds of the invention may be prepared as outlined below according to any of methods A-C. However, the invention is not limited to these methods, the compounds may  
 5 also be prepared as described for structurally related compounds in the prior art.

A. The compounds of the invention of formula I wherein A is S or O, B is C or CH can be prepared by a condensation reaction of a carbonyl compound of the formula II



10

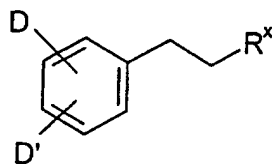
with a compound of the formula



and if desired, followed by reduction of the obtained compound.

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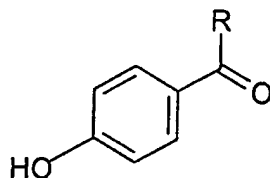
The compound of the formula II is prepared by coupling a compound of formula



20 with a compound of formula



15

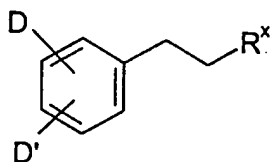


at, for example alkylation conditions or by a Mitsunobu reaction (Tsunoda, Tetr. Lett. 34,  
1639-42 (1993), when necessary followed by modifications of the D-group as described in  
5 the experimental section.

The group  $R^x$  can be a sulfonate, a halogen or an alcohol.

The compound of formula

10



can be prepared by standard procedures known to anyone skilled in the art, from commercial  
15 available starting materials.

In the condensation step an approximately equimolar amounts of reactants are heated in the  
presence of a mild base, such as sodium acetate or piperidine acetate to provide the olefin  
compound of formula I wherein  $\equiv$  is a double bond. This step may be carried out in  
20 the presence of a reaction inert solvent or in the absence of solvent at a temperature which  
is sufficiently high to cause at least partial melting of the reaction mixture. A preferred  
such temperature is in the range of 100°C to 250°C.

In a typical such reaction the aldehyde or ketone starting material and thiazolidinedione/  
25 oxazolidinedione are combined in approximately equimolar amounts with molar excess,

pref. 1-4 fold molar excess, of anhydrous sodium acetate and the mixture is heated, at a temperature high enough to effect melting and if necessary under vacuum. The olefin (compound of formula I wherein  $\text{====}$  is a double bond) can then be isolated by mixing with water or acetone and followed by filtration of the precipitate, to obtain the crude product which is purified if desired, e.g. by recrystallization or by standard chromatographic methods.

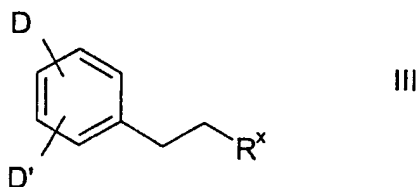
This reaction also takes place conveniently in a solvent such as toluene in presence of piperidine acetate. The resulting solution is refluxed with water separation in a Dean-Stark apparatus. The solution is then cooled and the olefin product isolated and purified, by standard methods.

The reduction of the olefin may be carried out by employing a wide variety of reducing agents which are known to reduce carbon-carbon double bonds, such as catalytic hydrogenation in the presence of an appropriate catalyst, magnesium or sodium amalgam in a lower alcohol such as methanol, or hydrogen transfer reagents such as diethyl-2,5-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

The catalytic hydrogenation can be conducted in alcohol, cellosolves, protic polar organic solvents, ethers, alkoxyalkanes, lower alifatic acids, and particularly methanol, ethanol, methoxyethanol, dimethylformamide, tetrahydrofurane, dioxane, dimethoxyethane, ethylacetate or acetic acid is preferably used alone or in mixture. Examples of the catalyst used include palladium black, palladium on carbon and platinum oxide. This reaction can proceed at normal temperature under normal pressure or at elevated temperature under increased pressure depending on the reactivity of the aimed reaction.

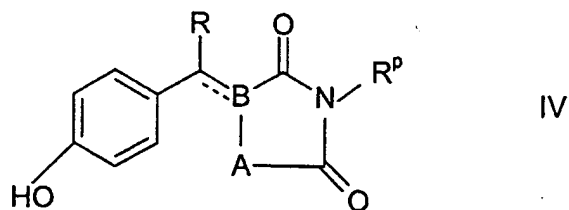
In case of hydrogen transfer reaction with diethyl-2,5-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate the reaction is conducted by mixing equimolar amounts of reactans and warming the mixture to melting (140-250°C) under inert atmosphere or under vacuum.

B. The compounds of the invention of formula I can be prepared by reaction of a compound of the formula



5

with a compound of the formula



- 10 wherein D, D', R, A and B are as defined above,  $R^x$  is a leaving group or a -OH group and  $R^p$  is hydrogen or a protecting group, either by an alkylation reaction or a Mitsunobu reaction, when necessary followed by deprotection of the protective group  $R^p$ .

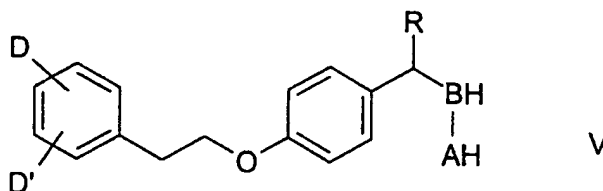
- In an alkylation reaction the leaving group  $R^x$  can be a sulfonate such as mesylate,  
 15 nosylate, tosylate, or a halogen, such as bromine or iodine. The compounds of formula III and IV in approximately equimolar amounts or with an excess of either compound are heated to reflux temperature in an inert solvent, such as isopropanol or acetonitrile, in the presence of a base, such as potassium carbonate or cesium carbonate.

- 20 The mixture is refluxed for the necessary time, typically between 0.5 h to 24 h, the work up procedure usually includes filtration, for removal of solid salt, evaporation and extraction with water and an organic solvent such as dichloromethane, ethylacetate, or diethyl ether. The crude product is purified if desired e.g. by recrystallization or by standard chromatographic methods.

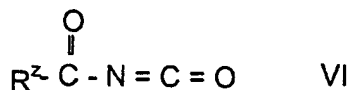
The Mitsunobu reaction can be carried out according to standard methods.

In a typical Mitsunobu reaction a compound of formula III, wherein the group  $R^x$  is a hydroxyl group, and a compound of formula IV are mixed in an inert solvent, such as chloroform or dichloromethane, in approximately equimolar amounts. A slight molar excess, 1-4 equivalents, of azodicarboxylate, such as DEAD (diethyl azodicarboxylate) or ADDP (azodicarbonyl dipiperidine) and a phosphine (1-4 equivalents), such as tributylphosphine or triphenylphosphine are added and the reaction is stirred at a temperature high enough - for example room temperature - and a time long enough (1-24 hours) to obtain the crude product, which can be worked up with standard literature methods and if desired purified, e.g. by standard chromatographic methods.

C. The compounds of the invention of the formula I wherein A is O, B is N, and  $\equiv$  is a single bond can be prepared by reaction of a compound of the formula



with a compound of the formula VI

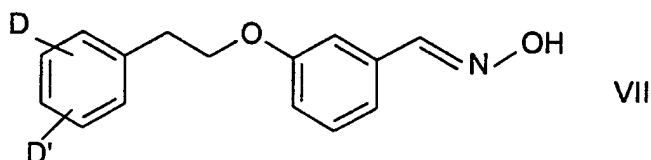


wherein D, D', R, A and B are as defined above and  $R^Z$  is a halogen, preferably chlorine.

In a typical reaction the compound of formula VI is added to a cool solution of a compound of formula V in an inert solvent, such as tetrahydrofuran or diethylether, preferentially at a slow enough speed to keep the temperature below  $-5^{\circ}\text{C}$ . The reaction mixture is stirred at a temperature between  $-10^{\circ}\text{C}$  and room temperature for an appropriate time.

The reaction can be worked up by acidification, e.g. by pouring it onto a water solution of hydrochloric acid, and extraction with the aid of an organic solvent. The crude product of the desired compound can be purified if desired by crystallization or standard chromatographic methods.

The compounds of formula V can be prepared by reduction of a compound of formula VII



in a solvent such as tetrahydrofuran and/or methanol, using an excess of a reducing agent, such as sodium cyanoborohydride.

In a typical such reaction an excess of the reducing agent, e.g. sodium cyanoborohydride, is added to a solution of a compound of formula VII in methanol and tetrahydrofuran.

Hydrochloric acid in a solvent, such as dioxan can be added.

The reaction can be worked up according to literature and if necessary purified by standard chromatographic methods to give the compound of formula V.

The compound of formula VII can be prepared by reacting a compound of formula II with hydroxyl amine.

A typical such reaction is performed by adding an excess of hydroxyl amine hydrochloride and a base, such as sodium acetate in water, to a solution of a compound of formula II in a solvent, such as ethanol. The reaction can be performed at a temperature of 50°C for 1.5 hours.

The crude product can be purified by crystallization to give the compound of formula VII.

The compound of formula II can be prepared as described in method A.

#### Pharmaceutical preparations

15

The compounds of the invention will normally be administered via the oral, parenteral, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free acid, or a pharmaceutical acceptable organic or inorganic base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

The compounds of the invention may also be combined with other therapeutic agents which are useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidemias, dyslipidemias, diabetes and obesity.

Suitable daily doses of the compounds of the invention in therapeutical treatment of humans are about 0.01-10 mg/kg body weight.

30

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

5

#### Pharmacological properties

The present compounds of formula (I) are readily adapted to clinical use for treatment of clinical conditions associated with reduced sensitivity to insulin (insulin resistance) and  
10 other metabolic disorders. These clinical conditions will include but will not be limited to abdominal obesity, arterial hypertension, hyperinsulinemia, hyperglycemia, dyslipidemia, particularly elevated triglycerides and non esterified fatty acids in blood associated with elevated VLDL and reduced HDL lipoproteins. Treatment with the present compounds is expected to lead to lower cardiovascular morbidity and mortality i.e. reduced incidence of  
15 ischemic heart disease including myocardial infarction, cerebrovascular disease including stroke as well as peripheral atherosclerotic disease including renal disease and peripheral arterial insufficiency of the extremities.

#### Working examples

20

##### **Example 1.**

##### **4-Cyanophenethyl methanesulfonate**

3.7 g (25 mmole) p-cyanophenethylalcohol was dissolved in 15 ml dichloromethane, 5.2  
25 ml (87.5 mmole) triethylamine was added and the mixture was cooled on an ice bath. 2.52 ml (32.5 mmole) methanesulfonyl chloride in 5 ml dichloromethane was slowly added at 0-7° C. The reaction was allowed to reach room temperature and then stirred at room temperature. The reaction mixture was washed with cooled 2 N hydrochloric acid, water, dried (sodium sulphate), filtered and the solvent was evaporated in vacuo to give 5.3 g  
30 (yield 95 %) of 4-cyanophenethyl methanesulfonate.

## 4-[2-(4-Formylphenoxy)ethyl]benzonitrile

8.55 g (38 mmole) 4-cyanophenethyl methanesulfonate, 4.64 g (38 mmole) p-  
5 hydroxybenzaldehyde and 18.7 g (57 mmole) cesium carbonate in 150 ml acetonitrile was  
refluxed over night. The salt was filtered off and the solvent evaporated in vacuo. The  
residue was treated with 2 M sodium hydroxide and dichloromethane. The organic phase  
was dried and evaporated in vacuo. Purification by chromatography on silica gel using  
dichloromethane as eluent gave 1.6 g (yield 17 %) of 4-[2-(4-  
10 formylphenoxy)ethyl]benzonitrile.

## 5-(4-[2-(4-Cyanophenyl)ethoxy]benzylidene) thiazolidine-2.4-dione

2.4 g (9,6 mmole) 4-[2-(4-formylphenoxy)ethyl]benzonitrile, 1.4 g (12 mmole) 2.4-  
15 thiazolidinedione and 1.96 g (24 mmole) sodium acetate was mixed and heated under  
vacuum to 140°C. The reaction mixture melted and was after 30 minutes removed from the  
heat. Water:acetone (2:1) was added and filtration followed by recrystallization in  
trifluoroacetic acid/acetic acid gave 1.79 g (yield 52 %) of 5-(4-[2-(4-cyanophenyl)  
ethoxy]benzylidene) thiazolidine-2.4-dione.

20

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 3.05-3.2 (tr, 2H), 4.22-4.36 (tr, 2H), 7.0-7.12 (d, 2H),  
7.45-7.58 (m, 4H), 7.72 (s, 1H), 7.72-7.82 (m, 2H).

<sup>13</sup>C-NMR (75 MHz; DMSO-d<sub>6</sub>): δ 35.0, 67.9, 109.5, 115.6, 119.2, 120.7, 125.9, 130.4,  
25 132.0, 132.4, 132.5, 144.7, 160.3, 167.8, 168.3.

## 5-([4-[2-(4-Cyanophenyl)ethoxy]phenyl]methyl) thiazolidine-2.4-dione

3.9 g (11 mmole) 5-(4-[2-(4-cyanophenyl)ethoxy]benzylidene) thiazolidine-2.4-dione and  
30 3.88 g (15 mmole) diethyl-1.4-dihydro-2.6-dimethyl-3.5-pyridine dicarboxylate were



mixed and heated to 210°C under vacuum for 1 hour. The solid material was dissolved in ethyl acetate, evaporated in vacuo, purified by chromatography on silica gel with first dichloromethane, then dichloromethane:diethyl ether (95:5) and finally dichloromethane:methanol (95:5) as eluents. Crystallization in acetone/water gave 0.65 g (yield 17 %)  
5 % of the desired product.

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 2.98-3.21 (m, 3H), 3.21-3.34 (dd, 1H), 4.16-4.24 (tr, 2H), 4.82-4.89 (dd, 1H), 6.22-6.90 (m, 2H), 7.09-7.17 (m, 2H), 7.49-7.58 (m, 2H), 7.74-7.82 (m, 2H).

10

**Example 2.**

5-([4-Benzyloxyphenyl]methyl)oxazolidine-2.4-dione

5.5 g (19.2 mmole) 2-hydroxy methyl 3-(4-benzyloxyphenyl) propionate, 1.98 g urea, 1.38  
15 g sodium methoxide, 4.9 ml methanol and 49 ml ethanol was stirred for 2 hours at room temperature, then refluxed over night. The reaction mixture was poured on to 305 ml 2 N hydrochloric acid. The product was extracted with ethyl acetate, washed with aqueous sodium bicarbonate, dried and the solvent was evaporated in vacuo. The crude product was purified by chromatography on silica gel using dichloromethane:methanol (95:5) as eluent  
20 to give 2.75 g (yield 48 %) of 5-([4-benzyloxyphenyl]methyl) oxazolidine-2.4-dione.

5-([4-Hydroxyphenyl]methyl) oxazolidine-2.4-dione

2.75 g (9.25 mmole) 5-([4-benzyloxyphenyl]methyl) oxazolidine-2.4-dione was  
25 hydrogenated at 50 psi over night in 1,4-dioxan using Pd/C as catalyst to give 1.8 g (yield 94 %) of 5-([4-hydroxyphenyl]methyl) oxazolidine-2.4-dione.

3-Triphenylmethyl-5-([4-hydroxyphenyl]methyl) oxazolidine-2.4-dione

30

0.33 g (1.18 mmole) triphenylmethyl chloride was added to a solution of 0.245 g (1.18 mmole) 5-([4-hydroxyphenyl]methyl) oxazolidine-2.4-dione, 0.165 ml (1.18 mmole) triethylamine, 5 ml dichloromethane and 5 ml dimethylformamide on an icebath. The temperature of the reaction mixture was allowed to reach room temperature. After 1.5 hours 0.05 ml more triethylamine was added. After 2 hours ethyl acetate and water were added and the phases were separated. The organic phase was dried (sodium sulfate), the solvent was evaporated and the crude product was purified by chromatography on silica gel using heptane:ethyl acetate (3:2) as eluent to give 0.32 g (yield 60 %) 3-triphenylmethyl-5-([4-hydroxyphenyl]methyl) oxazolidine-2.4-dione.

10

3-Triphenylmethyl-5-([4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl]methyl) oxazolidine-2.4-dione

15

0.28 g (0.623 mmole) 3-triphenylmethyl-5-([4-hydroxyphenyl]methyl) oxazolidine-2.4-dione was under argon atmosphere added to a cooled solution of 0.148 g (0.685 mmole) 2-[4-(methylsulfonyloxy)phenyl]-1-ethanol, 0.173 g (0.685 mmole) 1.1'-(azodicarbonyl)-dipiperidine and 0.18 g (0.685 mmole) triphenylphosphine in 6 ml dichloromethane. After stirring for 3 hours the reaction mixture was filtered and the crude product was purified by chromatography on silica gel using heptane:ethyl acetate (2:2) as eluent to give 0.215 g (yield 53 %) of 3-triphenylmethyl-5-([4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl]methyl) oxazolidine-2.4-dione.

20

5-([4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]phenyl]methyl) oxazolidine-2.4-dione

25

1 ml trifluoroacetic acid was added to a solution of 0.214 g (0.33 mmole) 3-triphenylmethyl-5-([4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl]methyl) oxazolidine-2.4-dione in 10 ml dichloromethane. After stirring for 45 minutes at room temperature 20 ml more of dichloromethane was added, the reaction mixture was washed twice with water, dried (sodium sulfate) and the solvent was evaporated in vacuo. The crude product was purified by chromatography on silica gel using heptane:ethyl acetate:acetic acid (10:10:1) as eluent

30

to give 0.118 g (yield 88 %) of 5-([4-[2-(4-methanesulfonyloxyphenyl)ethoxy]-phenyl]methyl) oxazolidine-2,4-dione.

<sup>13</sup>C-NMR (75 MHz; CD<sub>3</sub>OD): δ 36.0, 36.4, 37.4, 69.4, 82.6, 115.6, 123.2, 127.4, 131.7,  
5 132.0, 139.6, 149.6, 157.5, 159.6, 176.0.

### Example 3.

#### 2-[2,4-Di(benzyloxy)phenyl]-1-ethanol

10 10 ml (20 mmole) 2 M borane dimethyl sulfide complex in diethyl ether was slowly added to 6.3 g (18,1 mmole) 2,4-dibenzyloxyphenyl acetic acid dissolved in 50 ml dry tetrahydrofuran cooled on an ice bath under nitrogen and then stirred for 7 days at room temperature. The reaction was quenched with water and extracted with ethyl acetate, dried with magnesium sulfate and evaporated. The crude product was purified by chromatography on silica gel using dichloromethane/methanol as eluent to give 2.63 g of the desired  
15 product and a mixture of 2,4-dibenzyloxyphenyl acetic acid and the desired product. The mixture was dissolved in 100 ml ethyl acetate, 0.152 g (4 mmole) lithium aluminum hydride was added in portions and the mixture was stirred at room temperature for 6 hours. After 4 hours some more lithium aluminum hydride was added. The reaction was quenched  
20 with 1 % hydrochloric acid and the solution was filtered. The filtrate was dried with magnesium sulfate and evaporated in vacuo to give 1.3 g more of 2-[2,4-di(benzyloxy)phenyl]-1-ethanol (total yield 3.9 g, 64.4 %).

#### 2-(2,4-Dihydroxyphenyl)-1-ethanol

25 3.7 g (11.1 mmole) 2-[2,4-di(benzyloxy)phenyl]-1-ethanol was hydrogenated in 100 ml ethyl acetate using Pd/C (10 %) as catalyst. The reaction mixture was filtered and the filtrate was evaporated in vacuo to give 1.7 g (yield 99 %) of 2-(2,4-dihydroxyphenyl)-1-ethanol.

30 2,4-(Dimethylsulfonyloxy)phenethyl methanesulfonate

5.8 ml (41.5 mmole) triethylamine was added to a mixture of 1.7 g (11 mmole) 2-(2,4-dihydroxyphenyl)-1-ethanol in 100 ml dichloromethane. The mixture was cooled on an icebath and 3 ml (38.6 mmole) methanesulfonyl chloride was added slowly. The reaction mixture was stirred at room temperature for 5 h. As the reaction was not completed, 0.5 ml methanesulfonyl chloride was added and the mixture was stirred at room temperature over night but this gave no better result. The solvent was removed by evaporation in vacuo and 100 ml tetrahydrofuran, 2 ml triethylamine and 1 ml methanesulfonyl chloride were added and the mixture was stirred in room temperature for 1 hour. The solvent was removed by evaporation in vacuo, dichloromethane was added and the solution was washed with water, dilute sodium bicarbonate and brine and dried with magnesium sulfate. The solvent was evaporated in vacuo over night to give 4.4 g of an oil which was directly used in the next step.

15 4-[2-(4-Formylphenoxy)ethyl]-3-(methylsulfonyloxy)phenyl methanesulfonate

4.4 g (11 mmole) 2,4-di(methylsulfonyloxy)phenethyl methanesulfonate, 2.7 g (22.1 mmole) p-hydroxybenzaldehyde and 3.1 g (22.5 mmole) potassium carbonate in 150 ml acetonitrile was refluxed over night. The solvent was evaporated in vacuo. To the residue was added dichloromethane and water and the phases were separated. The organic phase was washed with water, dried with magnesium sulfate and the solvents were evaporated in vacuo. The residue was purified by chromatography on silica gel twice, using first dichloromethane/methanol and then ethyl acetate/hexane as eluents, to give 0.38 g of 4-[2-(4-formylphenoxy)ethyl]-3-(methylsulfonyloxy)phenyl methanesulfonate. One of the isolated byproducts was mesylated and worked up as above to give 0.55 g more of the product (yield in 2 steps 20.4 %).

5-(4-[2-(2,4-Dimethanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2,4-dione

0.887 g (2.14 mmole) 4-[2-(4-formylphenoxy)ethyl]-3-(methylsulfonyloxy)phenyl methanesulfonate was dissolved in 8 ml dichloromethane. 0.314 g (2.68 mmole) 2,4-thiazolidinedione and 0.439 g (5.35 mmole) sodium acetate were added and everything was mixed together. The solvent was evaporated in vacuo and the mixture was heated under vacuum to 175°C and kept at this temperature for 20 minutes (the mixture melted at ca. 100°C). After cooling the reaction mixture was stirred in water and acetone. Acetic acid was added and the precipitate was collected by filtration, washed with acetone/water, pure water and dried to give 0.76 g (yield 69 %) of 5-(4-[2-(2,4-dimethanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2,4-dione.

10

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 3.1-3.23 (tr, 2H), 3.42 (s, 3H), 3.53 (s, 3H), 4.24-4.36 (tr, 2H), 7.06-7.15 (m, 2H), 7.3-7.39 (m, 1H), 7.42-7.48 (m, 1H), 7.5-7.59 (m, 2H), 7.61-7.69 (m, 1H), 7.75 (s, 1H).

15 5-([4-[2-(2,4-Dimethanesulfonyloxyphenyl)ethoxy]phenyl]methyl) thiazolidine-2,4-dione

0.718 g (1.4 mmole) 5-(4-[2-(2,4-dimethanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2,4-dione was hydrogenated over night in 100 ml ethyl acetate and 1 ml acetic acid with 1.4 g Pd/C (10 %) as catalyst. The catalyst was filtered off and the filtrate was washed with water, dried with magnesium sulfate and evaporated in vacuo to give 0.55 g (yield 76 %) of the desired product.

20 <sup>1</sup>H-NMR (300 MHz; CDCl<sub>3</sub>): δ 3.0-3.22 (m, 3H), 3.10 (s, 3H), 3.18 (s, 3H), 3.3-3.5 (dd, 1H), 4.1-4.25 (tr, 2H), 4.4-4.55 (dd, 1H), 6.75-6.9 (m, 2H), 7.05-7.17 (m, 2H), 7.17-7.27 (m, 1H), 7.33 (s, 1H), 7.41-7.52 (m, 2H), 8,5 (bs, 1H).

25 <sup>13</sup>C-NMR (75 MHz; CDCl<sub>3</sub>): δ 29.6, 37.59, 37.64, 38.5, 53.6, 66.8, 114.8, 116.7, 121.1, 128.0, 130.5, 131.2, 132.4, 147.5, 147.7, 157.9, 170.4, 174.1.

**Example 4.****4-(4-Methoxyphenylsulfonyloxy)phenethyl 4-methoxy-1-benzenesulfonate**

2.76 g (20 mmole) p-hydroxyphenethyl alcohol was dissolved in 80 ml dichloromethane. 6  
5 g triethylamine, 8.5 g (41 mmole) 4-methoxybenzenesulfonyl chloride and 0.2 g 4-  
dimethyl-aminopyridine were added. The mixture was stirred over night at room  
temperature and filtered through silica gel with dichloromethane as eluent to give 8.5 g  
(yield 89 %) of 4-(4-methoxyphenylsulfonyloxy)phenethyl 4-methoxy-1-benzenesulfonate.

10 **4-[2-(4-Formylphenoxy)ethyl]phenyl 4-methoxy-1-benzenesulfonate**

A mixture of 8.5 g (17.8 mmole) 4-(4-methoxyphenylsulfonyloxy)phenethyl 4-methoxy-1-  
benzenesulfonate, 2.16 g (17.7 mmole) 4-hydroxybenzaldehyde and 10 g (72.5 mmole)  
potassium carbonate in 60 g acetonitrile was refluxed over night. The salt was filtered off  
15 and the solvent was evaporated. The crude product was purified on silica gel using  
dichloromethane as eluent to give 7.4 g of 4-[2-(4-formylphenoxy)ethyl]phenyl 4-  
methoxy-1-benzenesulfonate (slightly polluted with the corresponding styrene product).

20 **5-(4-[2-(4-(4-Methoxyphenylsulfonyloxy)phenyl)ethoxy]benzylidene) thiazolidine-2,4-  
dione**

A mixture of 2 g (4.85 mmole) 4-[2-(4-formylphenoxy)ethyl]phenyl 4-methoxy-1-  
benzenesulfonate and 0.8 g (6.8 mmole) 2,4-thiazolidinedione, 0.4 g piperidine, 0.3 g  
acetic acid and 20 ml toluene was refluxed with water separation in a Dean-Stark apparatus  
25 for 2.5 hours. The solvent was evaporated in vacuo, the residue was dissolved in  
dichloromethane and washed with potassium hydrogensulfate solution and with water,  
dried with magnesium sulfate, filtered and the solvent was concentrated in vacuo. 1.2 g of  
crystals were filtered off and the mother liquid was purified by chromatography on silica  
gel using dichloromethane-/diethylether (gradient) as eluent to give 0.5 g more, totally 1.7

g (yield 69 %) of 5-(4-[2-(4-(4-methoxyphenylsulfonyloxy)phenyl)ethoxy]benzylidene) thiazolidine-2,4-dione.

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 2.9-3.1 (tr, 2H), 3.84 (s, 3H), 4.1-4.3 (tr, 2H), 6.8-7.0 (m, 2H), 7.0-7.2 (m, 2H), 7.2-7.37 (m, 2H), 7.37-7.6 (m, 2H), 7.6-7.85 (m, 3H).

5-([4-[2-(4-(4-Methoxyphenylsulfonyloxy)phenyl)ethoxy]phenyl]methyl) thiazolidine-2,4-dione

1.2 g (2.35 mmole) 5-(4-[2-(4-(4-methoxyphenylsulfonyloxy)phenyl)ethoxy]benzylidene) thiazolidine-2,4-dione was mixed with 200 ml warm ethyl acetate, 2 ml acetic acid and 1.2 g Pd/C (5%, 50 % water) and hydrogenated for 4 hours at room temperature. 1.2 g more of the catalyst was added after 2 hours. The catalyst was filtered off and the solvent was evaporated in vacuo. The crude product was purified by chromatography on silica gel using dichloromethane/diisopropyl ether (gradient) as eluent to give 0.5 g of the desired product.

<sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): δ 3.02-3.14 (m, 3H), 3.40-3.48 (dd, 1H), 3.89 (s, 3H), 4.09-4.15 (tr, 2H), 4.47-4.53 (dd, 1H), 6.79-6.85 (m, 2H), 6.90-7.0 (m, 4H), 7.1-7.16 (M, 2H), 7.17-7.23 (m, 2H), 7.73-7.78 (m, 2H).

<sup>13</sup>C-NMR (75 MHz; CDCl<sub>3</sub>): δ 35.0, 37.7, 53.6, 55.7, 68.2, 114.3, 114.8, 122.4, 126.7, 127.8, 130.1, 130.3, 130.7, 137.3, 148.2, 158.1, 164.0, 170.5, 174.3.

#### Example 5.

4-(Methylsulfonyloxy)phenethyl methanesulfonate

25

27.3 g (0.27 mmole) triethylamin and a solution of 27.2 g (0.239 g mmole) methane sulfonyl chloride in dichloromethane were added to a solution of 15 g (0.108 mmole) p-hydroxyphenethyl alcohol in dichloromethane at 0°C. The reaction was allowed to reach room temperature, then stirred at room temperature and followed by TLC. The reaction mixture was filtered and the filtrate was washed with water. The solution was dried with

30

sodium sulfate and then evaporated in vacuo to give 28 g (yield 88%) of 4-(methylsulfonyloxy)phenethyl methanesulfonate.

4-[2-(4-Formylphenoxy)ethyl]phenyl methanesulfonate

5  
30 g (0.102 mole) 4-(methylsulfonyloxy)phenethyl methanesulfonate was dissolved in acetonitrile and slowly added to a mixture of 31.1 g (0.255 mole) p-hydroxybenzaldehyde and 41.46 g (0.3 mole) potassium carbonate in acetonitrile and refluxed until the starting material was consumed. The salt was filtered off, the solvent evaporated in vacuo,  
10 dichloromethane was added and the organic phase was washed with water. After evaporation of the solvent, purification by chromatography on silica gel using dichloromethane as eluent gave 21.6 g (yield 66 %) of 4-[2-(4-formylphenoxy)ethyl]phenyl methanesulfonate.

15 5-(4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2.4-dione

1.5g (4.7 mmole) 4-[2-(4-formylphenoxy)ethyl]phenyl methanesulfonate, 0.68 g (5.8 mmole) 2.4-thiazolidinedione and 0.96 g (11.8 mmole) sodium acetate were mixed and heated under vacuum to 155°C. The reaction mixture melted and was removed from the  
20 heat after 15 minutes. Water/acetone (2:1) was added and the mixture was stirred for 1 h. Filtration gave 1.67 g (yield 83 %) of 5-(4-[2-(4-methanesulfonyloxyphenyl)-ethoxy]benzylidene) thiazolidine-2.4-dione as yellow crystals.

<sup>1</sup>H-NMR (400 MHz; DMSO-d<sub>6</sub>): δ 3.02-3.09 (tr, 2H), 3.32 (s, 3H), 4.22-4.28 (tr, 2H),  
25 7.03-7.09 (m, 2H), 7.24-7.29 (m, 2H), 7.38-7.44 (m, 2H), 7.47-7.52 (m, 2H), 7-68 (s, 1H).  
<sup>13</sup>C-NMR (75 MHz; DMSO-d<sub>6</sub>): δ 33.9, 37.2, 68.0, 115.3, 120.2, 122.0, 125.5, 130.5, 131.7, 132.0, 137.4, 147.6, 160.6, 167.3, 167.8.

5-([4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]phenyl]methyl) thiazolidine-2.4-dione



98 g (0.23 mole) 5-(4-[2-(4-methanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2.4-dione and 89 g (0.35 mole) diethyl-1.4-dihydro-2.6-dimethyl-3.5-pyridine dicarboxylate was heated under reduced pressure until it melted (160°C). The reaction mixture was allowed to stay at this temperature for 5 hours. The reaction mixture was then taken off the heat and toluene was added when the temperature was below 100°C. The crystals were collected and washed with diethyl ether and recrystallized in toluene to give 77 g (yield 79 %) of the desired product.

<sup>1</sup>H-NMR (600 MHz; CDCl<sub>3</sub>): δ 3.05-3.105 (m, 3H), 3.12 (s, 3H), 3.38-3.45 (m, 1H), 4.11-4.17 (tr, 2H), 4.45-4.50 (m, 1H), 6.78-6.84 (m, 2H), 7.09-7.14 (m, 2H), 7.19-7.25 (m, 2H), 7.29-7.34 (m, 2H).

<sup>13</sup>C-NMR (150 MHz; CDCl<sub>3</sub>): δ 35.1, 37.3, 37.7, 53.6, 68.2, 114.8, 122.0, 127.8, 130.4, 130.5, 137.8, 147.6, 158.2, 170.0, 173.8.

#### Example 6

##### 2-[4-(tert-Butoxycarbonylamino)phenyl]-1-ethanol

5 g (36 mmole) 4-aminophenethyl alcohol was dissolved in tetrahydrofuran and cooled on an icebath. 7.95 g (36 mmole) di-tert-butyl dicarbonate was added in portions. The reaction mixture was stirred at room temperature over night. The solvent was evaporated in vacuo to give 8 g (yield 94 %) of 2-[4-(tert-butoxycarbonylamino)phenyl]-1-ethanol as a white powder.

##### 4-(tert-Butoxycarbonylamino)phenethyl 3-nitro-benzenesulfonate

4.25 g (42 mmole) triethylamine was added to 10 g (42 mmole) 2-[4-(tert-butoxycarbonylamino)phenyl]-1-ethanol dissolved in dichloromethane. The reaction mixture was cooled to -25°C and 9.34 g (42 mmole) 3-nitrobenzenesulfonyl chloride was added in portions. The reaction mixture was poured on to icewater, the phases were separated and the organic phase was dried (sodium sulfate), filtered and the solvent was

evaporated in vacuo. The residue was purified by chromatography on silica gel using dichloromethane as eluent to give 8.3 g (yield 47 %) 4-(tert-butoxycarbonylamino)-phenethyl 3-nitro-benzenesulfonate as yellow crystals.

5 tert-Butyl N-{4-[2-(4-formylphenoxy)ethyl]phenyl} carbamate

26.7 g (63 mmole) 4-(tert-butoxycarbonylamino)phenethyl 3-nitro-benzenesulfonate, 8.5 g (69 mmole) p-hydroxybenzaldehyde, 9.54 g (69 mmole) potassium carbonate and acetonitrile was refluxed for 3 hours and thereafter stirred over night at room temperature.

10 The precipitate was filtered off and the solvent was evaporated. Dichloromethane was added and the organic phase was washed with saturated sodium carbonate and thereafter with sodiumhydroxide (0.1 M), dried (sodium sulfate), filtered and the solvent was evaporated to give 17 g (yield 79 %) of tert-butyl N-{4-[2-(4-formylphenoxy)ethyl]phenyl} carbamate.

15

4-[2-(4-Aminophenyl)ethoxy]benzaldehyde

5g (14.6 mmole) tert-butyl N-{4-[2-(4-formylphenoxy)ethyl]phenyl} carbamate was deprotected in ethyl acetate saturated with hydrochloric acid at room temperature over night. The product precipitated and filtration yielded 5 g (100 %) of 4-[2-(4-aminophenyl)ethoxy]benzaldehyde x HCL. The product contained some solvent, but was used without further purification.

20

N-{4-[2-(4-Formylphenoxy)ethyl]phenyl} methanesulfonamide

25

6.75 g (64 mmole) triethylamine was added to 5 g (14,6 mmole) 4-[2-(4-aminophenyl)ethoxy]benzaldehyde x HCl (containing some ethyl acetate) in dichloromethane. 3.65 g (32 mmole) methanesulfonyl chloride was slowly added at 0°C, and the mixture was stirred over the weekend. A yellow precipitate was filtered off and the filtrate was washed with water. The organic phase was dried (sodium sulfate), filtered and

30

the solvent was evaporated. The residue contained some triethylamine and therefor it was dissolved in dichloromethane and washed with 2 M hydrochloric acid and brine, dried and filtered and the solvent was evaporated to give 1.6 g (yield 34 %) of N-{4-[2-(4-formylphenoxy)ethyl]phenyl} methanesulfonamide as a yellow powder.

5

5-(4-[2-(4-Methanesulfonylamino-phenyl)ethoxy]benzylidene) thiazolidine-2.4-dione

1.6 g (5 mmole) N-{4-[2-(4-formylphenoxy)ethyl]phenyl} methanesulfonamide, 0.73 g (6.25 mmole) 2-4- thiazolidinedione and 1.025 g (12.5 mmole) sodium acetate were mixed and heated to 140°C on an oil bath under vacuum (it melted at 130°C). It was kept at 140°C for 20 minutes and thereafter taken off the heat. When the temperature was low enough water:acetone (2:1) was added to dissolve the reaction product. Acetone was evaporated in vacuo, acetic acid was added and the obtained crystals were filtered off and recrystallized in dichloromethane to give 0.83 g (yield 40 %) of 5-(4-[2-(4-methanesulfonylamino-phenyl)ethoxy]benzylidene) thiazolidine-2.4-dione.

15

<sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 2.95 (s, 3H), 3.06-3.15 (tr, 2H), 4.25-4.34 (tr, 2H), 7.07-7.14 (m, 2H), 7.25-7.38 (m, 4H), 7.51-7.59 (m, 2H), 7.72 (s, 1H).

<sup>13</sup>C-NMR (100 MHz; acetone-d<sub>6</sub>): δ 34.5, 38.05, 69, 115.5, 120.5, 121.5, 126, 130, 132, 132.5, 135, 137, 161, 167.5, 167.8.

20

5-([4-[2-(4-Methanesulfonylamino-phenyl)ethoxy]phenyl]methyl) thiazolidine-2.4-dione

25

0.83 g (2 mmole) 5-(4-[2-(4-methanesulfonylamino-phenyl)ethoxy]benzylidene) thiazolidine-2.4-dione and 0.65 g (2.6 mmole) diethyl-1.4-dihydro-2.6-dimethyl-3.5-pyridinedicarboxylate was mixed and heated to 145°C under vacuum. After 45 minutes at 145°C the reaction mixture was taken off the heat and toluene was added. The toluene solution was decanted off and the solid residue was purified by chromatography on silica

30

gel using dichloromethane:methanol 95:5 as eluent to give 0.25 g (yield 30 %) of the desired product.

<sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 2.97 (s, 3H), 3.03-3.10 (tr, 2H), 3.10-3.19 (dd, 1H),  
5 3.39-3.48 (dd, 1H), 4.16-4.24 (tr, 2H), 4.75-4.82 (dd, 1H), 6.87-6.94 (m, 2H), 7.19-7.26  
(m, 2H), 7.26-7.39 (m, 4H), 8.5 (bs, 1NH).

<sup>13</sup>C-NMR (100 MHz; acetone-d<sub>6</sub>): δ 35, 37, 39, 53, 69, 114.5, 120.7, 129, 130, 130.5, 135,  
137, 158.5, 171, 175.

10

#### Example 7.

5-(4-[2-(4-tert-Butyloxycarbonylamino)phenyl]ethoxy)benzylidene thiazolidine-2,4-dione

A solution of 3.41 g (10 mmole) tert-butyl N-{4-[2-(4-formylphenoxy)ethyl]phenyl}  
15 carbamate and 1.29 g (11 mmole) 2,4-thiazolidinedione in toluene containing a catalytic  
amount of piperidinium acetate was refluxed in a Dean-Stark water trap for 3 hours. The  
reaction was followed by TLC and more 2,4-thiazolidinedione was added during the  
reaction time. The solution was cooled to room temperature filtered and the precipitate was  
refluxed in methanol. Another filtration gave 3.2 g (yield 72.6 %) 5-(4-[2-(4-tert-  
20 butyloxycarbonylamino)phenyl]ethoxy)benzylidene thiazolidine-2,4-dione as a light  
yellow, solid substance.

<sup>1</sup>H-NMR (500 MHz; DMSO-d<sub>6</sub>): δ 1.5 (s, 9H), 2.89-3.10 (tr, 2H), 4.13-4.32 (tr, 2H), 7.01-  
7.16 (m, 2H), 7.16-7.32 (m, 2H), 7.32-7.49 (m, 2H), 7.49-7.66 (m, 2H), 7.76 (s, 1H), 9.3  
25 (bs, 1NH).

<sup>13</sup>C-NMR (125 MHz; DMSO-d<sub>6</sub>): δ 28.3, 34.3, 68.8, 79, 115.6, 118.4, 120.5, 125.7,  
129.3, 131.7, 134.0, 132.3, 138.1, 153.0, 160.4, 167.7, 168.2

5-(-[4-[2-(4-tert-Butyloxycarbonylamino)phenyl]ethoxy]phenyl)methyl thiazolidine-2,4-  
30 dione

A solution of 0.5 g (1,14 mmole) 5-(4-[2-(4-tert-butyloxycarbonylaminophenyl)-ethoxy]benzylidene) thiazolidine-2,4-dione in ethylacetate was hydrogenated in the presence of 5% palladium on charcoal at room temperature and atmospheric pressure until  
5 hydrogen uptake ceased. The solution was filtered through celite, the filter pad was washed with ethyl acetate and the filtrate was evaporated to give 0.5 g (yield 99%) of 5-([4-[2-(4-tert-butyloxycarbonylaminophenyl)ethoxy]phenyl]methyl) thiazolidine-2,4-dione.

<sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): δ 1.5 (s, 9H), 3.0-3.14 (m, 3H), 3.40-3.48 (dd, 1H), 4.08-4.16  
10 (tr, 2H), 4.45-4.52 (dd, 1H), 6.55 (bs, 1NH), 6.79-6.87 (m, 2H), 7.08-7.15 (m, 2H), 7.15-7.23 (m, 2H), 7.23-7.34 (m, 2H).

#### Example 8.

##### 4-([3-Nitrophenylsulfonyl]oxy)phenethyl 3-nitrobenzenesulfonate

15 45 g (0.203 mole) 3-nitrobenzenesulfonyl chloride was added to a cooled solution of 13.8 g (0.1 mmole) p-hydroxyphenethyl alcohol and 25 g (0.248 mmole) triethylamine in 250 ml dichloromethane. The reaction mixture was stirred at room temperature for 1.5 hours. Dichloromethane and water were added and the phases separated. The organic phase was  
20 washed with dilute potassium hydrogen sulfate and water, dried (sodium sulfate), filtered and the solvent was evaporated in vacuo. Recrystallization in diisopropyl ether gave 48.8 g (yield 96 %) of 4-([3-nitrophenylsulfonyl]oxy)phenethyl 3-nitrobenzenesulfonate.

##### 4-[2-(4-Formylphenoxy)ethyl]phenyl 3-nitrobenzenesulfonate

25 A mixture of 32.5 g (64 mmole) 4-([3-nitrophenylsulfonyl]oxy)phenethyl 3-nitrobenzenesulfonate, 8 g (65 mmole) p-hydroxybenzaldehyde and 20 g (145 mmole) potassium carbonate in 300 ml acetonitrile was refluxed for 10 minutes, then stirred at room temperature over night and thereafter refluxed for 30 minutes. The salts were filtered  
30 off and the solvent evaporated in vacuo. Dichloromethane and water were added, the

phases were separated, the organic phase was dried and the solvent was evaporated in vacuo. Purification by chromatography on silica gel using dichloromethane as eluent and crystallization in diisopropyl ether gave 23.5 g (yield 86 %) of 4-[2-(4-formylphenoxy)ethyl]phenyl 3-nitrobenzenesulfonate.

5

5-(4-[2-(4-(3-Nitrophenylsulfonyloxy)phenyl)ethoxy]benzylidene) thiazolidine-2.4-dione

0.25 g (2.9 mmole) piperidine, 0.174 g (2.9 mmole) acetic acid, 120 ml toluene, 2.5 g (5.8 mmole) 4-[2-(4-formylphenoxy)ethyl]phenyl 3-nitrobenzenesulfonate and 0.86 g (7.3 mmole) 2,4-thiazolidinedione were refluxed with water separation in a Dean-Stark apparatus. When the reaction mixture was allowed to cool yellow crystals formed. The crystals were collected by filtration and stirred in methanol. Filtration gave 2 g (yield 65.5 %) of 5-(4-[2-(4-(3-nitrophenylsulfonyloxy)phenyl)ethoxy]benzylidene) thiazolidine-2.4-dione.

15

<sup>1</sup>H-NMR (400 MHz; DMSO-d<sub>6</sub>): δ 2.99-3.10 (tr, 2H), 4.18-4.30 (t, 2H), 7.01-7.08 (m, 4H), 7.31-7.37 (d, 2H), 7.48-7.54 (d, 2H), 7.72 (s, 1H), 7.91-7.97 (tr, 1H), 8.23-8.28 (m, 1H), 8.44-8.48 (tr (long range), 1H), 8.59-8.64 (m, 1H).

<sup>13</sup>C-NMR (100 MHz; DMSO-d<sub>6</sub>): δ 34.4, 68.5, 115.9, 120.9, 122.5, 123.4, 126.1, 130.0, 131.2, 132.21, 132.4, 132.5, 134.5, 136.2, 138.6, 147.8, 148.6, 160.5, 168.0, 168.4.

20

5-([4-[2-(4-(3-Nitrophenylsulfonyloxy)phenyl)ethoxy]phenyl]methyl) thiazolidine-2.4-dione

2.4 g (4.6 mmole) 5-(4-[2-(4-(3-nitrophenylsulfonyloxy)phenyl)ethoxy]benzylidene) thiazolidine-2.4-dione and 3.5 g (14 mmole) diethyl-1.4-dihydro-2.6-dimethyl-3.5-pyridine dicarboxylate were mixed and heated to 145°C under vacuum and after 1-2 hours the heat was removed. The solid material was dissolved in toluene, evaporated in vacuo and purified by chromatography on silica gel twice with ethyl acetate:petroleum ether 1:1 as eluents to give 1.002 g (yield 41 %) of the desired product.

30

<sup>1</sup>H-NMR (300 MHz; CDCl<sub>3</sub>): δ 2.92-3.15 (m, 3H), 3.35-3.55 (m, 1H), 4.0-4.25 (m, 2H), 4.40-4.55 (m, 1H), 6.65-6.85 (d, 2H), 6.85-7.0 (d, 2H), 7.0-7.15 (d, 2H), 7.15-7.33 (d, 2H), 7.67-7.83 (tr, 1H), 8.05-8.20 (d, 1H), 8.42-8.56 (d, 1H), 8.65 (s, 1H).

5 <sup>13</sup>C-NMR (75 MHz; CDCl<sub>3</sub>): δ 35.0, 37.7, 53.8, 68.1, 114.8, 122.0, 123.7, 128.0, 128.7, 130.4, 130.6, 130.8, 133.9, 137.4, 138.3, 147.7, 148.2, 158.0, 171.1, 174.8.

### Example 9

#### 2-(Methylsulfonyloxy)phenetyl methanesulfonate

10

9 g (79 mmole) methanesulfonyl chloride in dichloromethane was slowly added to a mixture of 5 g (36 mmole) o-hydroxyphenetyl alcohol and 7.99 g (79 mmole) triethylamine in dichloromethane at 0 -10°C. The temperature was then allowed to raise to room temperature and when the starting material was consumed the reaction mixture was  
15 poured on to hydrochloric acid/ice water. The phases were separated and the organic phase was washed with brine, dried and evaporated in vacuo. The residue crystallized on standing to give 9.4 g (yield 89 %) yellow crystals of 2-(methylsulfonyloxy)phenetyl methanesulfonate.

#### 20 2-[2-(4-Formylphenoxy)ethyl]phenyl methanesulfonate

9.2 g (31 mmole) 2-(methylsulfonyloxy)phenetyl methanesulfonate, 4.58 g (37.5 mmole) p-hydroxybenzaldehyde and 5.18 g (37.5 mmole) potassium carbonate were refluxed in acetonitrile for 4 hours and then stirred at room temperature over night. The salts were  
25 filtered off and the solvent was evaporated in vacuo. Sodium carbonate solution and dichloromethane was added to the residue. The phases were separated and the organic phase was dried and evaporated in vacuo. Chromatography on silica gel using dichloromethane as eluent gave a mixture of starting material and product. The reaction was restarted with 4.58 g p-hydroxybenzaldehyde and 5.18 g potassium carbonate and

worked up as above to give 1.7 g of pure 2-[2-(4-formylphenoxy)ethyl]phenyl methanesulfonate.

5-([4-[2-(2-Methanesulfonyloxyphenyl)ethoxy]phenyl]benzylidene) thiazolidine-2,4-dione

5

1.7 g (5.3 mmole) 2-[2-(4-formylphenoxy)ethyl]phenyl methanesulfonate, 0.77 g (6.6 mmole) 2,4-thiazolidinedione and 1.06 g (13.2 mmole) sodium acetate were heated to 130°C and allowed to stay at 130°C for 10 minutes. The reaction mixture was taken off the heat and water:acetone (2:1) was added, the formed solid material was stirred with water and acetic acid, the precipitate was collected by filtration and washed with diethyl ether and recrystallized in dichloromethane to give 1.63 g (yield 61 %) of 5-([4-[2-(2-methanesulfonyloxyphenyl)ethoxy]phenyl]benzylidene) thiazolidine-2,4-dione.

10

<sup>1</sup>H-NMR (500 MHz; DMSO-d<sub>6</sub>): δ 3.09-3.22 (tr, 2H), 3.49 (s, 3H), 4.23-4.39 (tr, 2H), 7.02-7.17 (m, 2H), 7.28-7.42 (m, 3H), 7.42-7.59 (m, 3H), 7.63 (s, 1H).

15

5-([4-[2-(2-Methanesulfonyloxyphenyl)ethoxy]phenyl]methyl) thiazolidine-2,4-dione

1.63 g (3.2 mmole) 5-([4-[2-(2-methanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2,4-dione and 1.23 g (4.8 mmole) diethyl-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate was mixed and heated to 150°C and kept at this temperature for 1 hour. The reaction mixture was cooled and purified by chromatography on silica gel using ethyl acetate:petroleum ether (1:2) as eluent to give 0.684 g (yield 51 %) of the desired product.

25

<sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): δ 3.03-3.15 (m, 1H), 3.15-3.26 (m, 5H), 3.38-3.48 (m, 1H), 4.16-4.23 (tr, 2H), 4.43-4.52 (m, 1H), 6.79-6.89 (d, 2H), 7.08-7.16 (d, 2H), 7.22-7.44 (m, 4H).

<sup>13</sup>C-NMR (100 MHz; DMSO-d<sub>6</sub>): δ 30.0, 37.7, 38.3, 53.7, 67.2, 122.2, 114.9, 127.4, 128.0, 128.2, 130.4, 131.4, 131.6, 147.7, 158.1, 170.8, 174.5.

30



**Example 10.****N-[4-(2-Hydroxyethyl)phenyl]-N<sup>1</sup>-methylurea**

5 34.3 (0.25 mole) p-aminophenethyl alcohol and 20 g (0.35 mmole) methyl isocyanate in 400 ml tetrahydrofuran was mixed and the formed white precipitate was collected by filtration to give 44.87 g (yield 92.4 %) of N-[4-(2-hydroxyethyl)phenyl]-N<sup>1</sup>-methylurea.

**4-(Methylaminocarbonylamino)phenethyl methanesulfonate**

10

47 g (0.412 mole) methanesulfonyl chloride in dichloromethane was added in small portions to a solution of 20 g (0.103 mole) N-[4-(2-hydroxyethyl)phenyl]-N<sup>1</sup>-methylurea and 41.7 g (0.412 mole) triethylamine in 500 ml dichloromethane at 0°C. After stirring at room temperature over night the reaction mixture was washed with 2 M hydrochloric acid and sodium bicarbonate. The organic phase was dried and concentrated by evaporation in vacuo and the formed precipitate was collected by filtration to give 8.81 g (yield 31 %) of 4-(methylaminocarbonylamino)phenethyl methanesulfonate.

15

**4-[2-(4-Formylphenoxy)ethyl]phenyl methylurea**

20

2 g (7.3 mmole) 4-(methylaminocarbonylamino)phenethyl methanesulfonate, 1.08 g (8.8 mmole) p-hydroxybenzaldehyde and 1.22 g (8.8 mmole) potassium carbonate in acetonitrile were refluxed over night. The salts were filtered off and the solvent was evaporated. The residue was dissolved in dichloromethane, washed with 2 M sodium hydroxide, dried and evaporated in vacuo. The solid residue was dissolved in water and acidified with 2 M hydrochloric acid, diethyl ether was added and the formed precipitate was collected by filtration to give 1 g (yield 46 %) of 4-[2-(4-formylphenoxy)ethyl]phenyl methylurea.

25

30 5-(4-[2-(4-Methylureidophenyl)ethoxy]benzylidene) thiazolidine-2,4-dione

3.5 g (12 mmole) 4-[2-(4-formylphenoxy)ethyl]phenyl methylurea, 3.44 (29 mmole) 2,4-thiazolidinedione, 0.1 g piperidine, 0.07 g acetic acid and toluene were refluxed with water separation in a Dean-Stark apparatus. When the reaction mixture was cooled to room temperature the formed precipitate was collected and washed with methanol to give 4.25 g (yield 89 %) of 5-(4-[2-(4-methylureidophenyl)ethoxy]benzylidene) thiazolidine-2,4-dione.

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 2.55-2.65 (d, 3H), 2.85-3.0 (tr, 2H), 4.1-4.3 (tr, 2H), 5.9-6.1 (m, 1NH), 7.02-7.22 (m, 4H), 7.22-7.42 (m, 2H), 7.42-7.61 (m, 2H), 7.73 (s, 1NH), 8.42 (s, 1NH).

<sup>13</sup>C-NMR (75 MHz; DMSO-d<sub>6</sub>): δ 26.1, 34.0, 68.5, 115.2, 117.6, 120.2, 125.3, 129.0, 130.2, 131.7, 132.0, 138.9, 155.8, 160.1, 167.4, 167.9.

5-([4-[2-(4-Methylureidophenyl)ethoxy]phenyl]methyl) thiazolidine-2,4-dione

1.2 g (3.02 mmole) 5-(4-[2-(4-methylureidophenyl)ethoxy]benzylidene) thiazolidine-2,4-dione was hydrogenated for 18 hours in 100 ml dimethylformamide and 10 ml acetic acid with 1 g Pd/C (10 %) as catalyst. The catalyst was filtered off and the solvent was evaporated in vacuo. Ethyl acetate was added and the product was extracted with potassium carbonate in water. A black precipitate was filtered off and the ethyl acetate phase was extracted with more potassium carbonate solution. The water phase was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was dried and evaporated in vacuo and recrystallized in methanol to give 0.71 g (yield 59%) of the desired product.

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 2.55-2.71 (d, 3H), 2.8-3.12 (m, 3H), 3.2-3.38 (m, 1H), 3.98-4.19 (tr, 2H), 4.75-4.92 (m, 1H), 5.84-6.0 (m, 1NH), 6.77-6.93 (m, 2H), 6.98-7.2 (m, 4H), 7.2-7.4 (m, 2H), 8.38 (s, 1NH), 12.01 (bs, 1NH).

<sup>13</sup>C-NMR (125 MHz; DMSO-d<sub>6</sub>): δ 26.4, 34.5, 36.5, 53.2, 68.5, 114.5, 118.0, 128.7, 129.3, 130.6, 130.8, 139.1, 156.1, 157.7, 171.9, 175.9.

5 **Example 11.**

4-[2-(4-Acetylphenoxy)ethyl]phenyl methanesulfonate

13.6 g (0.1 mole) p-hydroxyacetophenone, 29.4 g (0.1 mole) 4-(methylsulfonyloxy)-phenethyl methanesulfonate and 42.4 g (0.3 mole) potassium carbonate in acetonitrile were  
10 refluxed over night. The salts were filtered off and the solvent was evaporated in vacuo. The residue was crystallized in isopropylalcohol. The crystals were dissolved in dichloromethane, washed with diluted potassium carbonate, dried (magnesium sulfate), filtered and evaporated to give 22.7 g (yield 68 %) 4-[2-(4-acetylphenoxy)ethyl]phenyl methanesulfonate.

15

5-(1-[4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]phenyl]ethylene) thiazolidine-2.4-dione

10 g (29.9 mmole) 4-[2-(4-acetylphenoxy)ethyl]phenyl methanesulfonate and 3.85 g (32.9 mmole) 2.4-thiazolidinedione were heated to 140°C when the reaction mixture melted.  
20 4.76 g (38 mmole) sodium acetate was added and the reaction mixture was stirred under vacuum at elevated temperature until the reaction mixture was solid again. The heat was removed, water and acetone was added, acetone was evaporated in vacuo, and acidification with acetic acid gave crystals that were collected and recrystallized in acetic acid to give 5 g (yield 39 %) of 5-(1-[4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl]ethylene)  
25 thiazolidine-2.4-dione.

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 2.65 (s, 3H), 3.00-3.15 (t, 2H), 3.38 (s, 3H), 4.15-4.35 (t, 2H), 6.95-7.1 (d, 2H), 7.25-7.32 (d, 2H), 7.32-7.42 (d, 2H), 7.45-7.5 (d, 2H), 12.25 (bs, 1H).

<sup>13</sup>C-NMR (75 MHz; DMSO-d<sub>6</sub>): δ 21.6, 34.3, 37.5, 68.2, 114.9, 121.5, 122.3, 128.7, 130.8, 134.5, 137.8, 147.9, 149.1, 159.2, 167.3, 168.2.

5-(1-[4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]phenyl]ethyl) thiazolidine-2.4-dione

5

2.8 g (6.4 mmole) 5-(1-[4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl]ethylene) thiazolidine-2.4-dione and 1.6 g (6.4 mmole) diethyl-1.4-dihydro-2.6-dimethyl-3.5-pyridine dicarboxylate was mixed and heated to 170°C under vacuum. After 4 hours at 170°C the reaction mixture was taken off the heat, cooled to room temperature and  
10 purified by chromatography on silica gel using ethyl acetate and dichloromethane gradient as eluent to give 0.8 g (yield 29 %) of a diastereomeric mixture of the desired product.  
<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 1.2-1.4 (2 x d(diastereomers), 3H), 2.95-3.15 (tr, 2H), 3.35 (s, 3H), 3.5-3.7 (2 x m(diastereomers), 1H), 4.1-4.25 (tr, 2H), 4.82-4.95 (m, 1H), 6.8-6.95 (m, 2H), 7.1-7.23 (m, 2H), 7.23-7.34 (m, 2H), 7.34-7.5 (m, 2H).

15

### Example 12.

2-(4-Methylcarbonyloxyphenyl)-1-ethanol

5.6 g (0.1 mole) potassium hydroxide in 10 ml water was added to a cooled solution of  
20 13.8 g (0.1 mole) p-hydroxyphenethyl alcohol in 50 ml tetrahydrofuran. 10.2 g (0.1 mole) acetic anhydride was slowly added under stirring. After 2 hours diethyl ether and water were added. The phases were separated and the organic phase was dried, filtered and evaporated in vacuo. The product contained 15 % starting material and was therefore redissolved in diethyl ether and washed twice with dilute sodium carbonate. Drying,  
25 filtration and evaporation of solvents in vacuo gave 12 g (yield 67 %) of 2-(4-methylcarbonyloxyphenyl)-1-ethanol which was used without further purification.

4-(Methylcarbonyloxy)phenethyl methanesulfonate

55 g (0.305 mole) 2-(4-methylcarbonyloxyphenyl)-1-ethanol and 34.4 g (0.341 mole) triethylamine in 300 ml dichloromethane were cooled on an ice bath. 38.5 g (0.336 mole) methanesulfonyl chloride was slowly added. The ice bath was removed and the mixture was stirred for 3 hours at room temperature. Water was added and the phases were separated. The organic phase was washed with saturated sodium hydrogen bicarbonate and brine, dried (magnesium sulfate), filtered and evaporated in vacuo to give 76.6 g (yield 97 %) of 4-(methylcarbonyloxy)phenethyl methanesulfonate.

#### 4-[2-(4-Formylphenoxy)ethyl]phenyl acetate

10

10.3 g (39.9 mmole) 4-(methylcarbonyloxy)phenethyl methanesulfonate, 5.37 g (44 mmole) p-hydroxybenzaldehyde and 10 g (72.5 mmole) potassium hydroxide were refluxed in 100 ml acetonitrile for 2 hours. The salts were filtered off and the solvents was evaporated. The residue was dissolved in ethyl acetate and washed with water 3 times, dried and evaporated in vacuo to give 10.8 g (yield 95 %) of 4-[2-(4-formylphenoxy)ethyl]phenyl acetate.

#### 4-[2-(4-Hydroxyphenyl)ethoxy]benzaldehyde

Ammonium hydroxide was added to a solution of 2.0 g (7 mmole) 4-[2-(4-formylphenoxy)ethyl]phenyl acetate in methanol. When the starting material was consumed the solvent was evaporated in vacuo. 0.5 M hydrochloric acid was added and the product was extracted with diethyl ether and dichloromethane, dried, filtered and evaporated to give 1.6 g (yield 93 %) of 4-[2-(4-hydroxyphenyl)ethoxy]benzaldehyde

<sup>1</sup>H-NMR (400 MHz; DMSO-d<sub>6</sub>): δ 2.95-3.05 (tr, 2H), 4.22-4.32 (tr, 2H), 6.72-6.78 (m, 2H), 7.1-7.2 (m, 4H), 7.88-7.94 (m, 2H), 9.23 (s, 1H), 9.91 (s, 1H)  
<sup>13</sup>C-NMR (100 MHz; DMSO-d<sub>6</sub>): δ 34.4, 69.5, 115.4, 115.6, 130.3, 132.2, 156.4, 164.0.

#### 4-[2-(4-Formylphenoxy)ethyl]phenyl N-(tert-butyl)carbamate

30

0.5 g (2.1 mmole) 4-[2-(4-hydroxyphenyl)ethoxy]benzaldehyde was dissolved in tetrahydrofuran, cooled to 0°C and 0.092 g (2.1 mmole) sodium hydride in tetrahydrofuran was added. The reaction mixture was stirred until gas development ceased, then 0.4 g (4 mmole) tert-butyl isocyanate in tetrahydrofuran was added and the temperature was  
5 allowed to raise to room temperature. The reaction was followed by TLC. More 0.4 g (4 mmole) tert-butyl isocyanate was added. After 3 days the reaction was quenched with ice and sodium hydroxide (aq), extracted with dichloromethane, dried and evaporated. Purification by chromatography on silica gel using ethyl acetate:petroleum ether (1:2) as eluent gave 0.6 g (yield 84 %) of 4-[2-(4-formylphenoxy)ethyl]phenyl N-(tert-  
10 butyl)carbamate.

5-(4-[2-(4-tert-Butylaminocarbonyloxyphenyl) ethoxy]benzylidene) thiazolidine-2,4-dione

3.5 g (10.2 mmole) 4-[2-(4-formylphenoxy)ethyl]phenyl N-(tert-butyl)carbamate, 3 g (25.5  
15 mmole) 2,4-thiazolidindione, 0.1 g piperidine and 0.07 g acetic acid in toluene was refluxed with water separation in a Dean-Stark apparatus. The solvent was evaporated in vacuo, acetone and water was added and the formed precipitate was filtered off to give 2 g (yield 45 %) of 5-(4-[2-(4-tert-butylaminocarbonyloxyphenyl) ethoxy]benzylidene) thiazolidine-2,4-dione.

20

<sup>1</sup>H-NMR (500 MHz; DMSO-d<sub>6</sub>): δ 1.24 (s, 9H), 2.96-3.07 (tr, 2H), 4.18-4.28 (tr, 2H), 6.95-7.0 (m, 2H), 7.04-7.1 (m, 2H), 7.25-7.3 (m, 2H), 7.47 (s, 1H), 7.48-7.53 (m, 2H), 7.7 (s, 1NH).

25 5-([4-[2-(4-tert-Butylaminocarbonyloxyphenyl) ethoxy]phenyl]methyl) thiazolidine-2,4-dione

1 g (2.27 mmole) 5-(4-[2-(4-tert-butylaminocarbonyloxyphenyl) ethoxy]benzylidene) thiazolidine-2,4-dione was hydrogenated on Pd/C (5%) in ethyl acetate at atmospheric

pressure over night. The catalyst was filtered off and the solvent was evaporated in vacuo to give 1 g (yield 99 %) of the desired product.

<sup>1</sup>H-NMR (400 MHz; DMSO-d<sub>6</sub>): δ 1.25 (s, 9H), 2.95-3.08 (m, 3H), 3.23-3.34 (m, 1H),  
5 4.08-4.17 (tr, 2H), 4.30-4.38 (m, 1H), 6.83-6.89 (m, 2H), 6.95-7.01 (m, 2H), 7.09-7.15 (m,  
2H), 7.25-7.31 (m, 2H), 7.49 (s, 1NH), 12.01 (bs, 1H).

<sup>13</sup>C-NMR (100 MHz; DMSO-d<sub>6</sub>): δ 28.9, 34.7, 36.8, 50.2, 53.5, 68.5, 114.8, 122.2, 129.1,  
130.1, 130.8, 135.2, 150.0, 153.2, 157.9, 172.1, 176.2.

10 **Example 13.**

Methyl N-[4-(2-hydroxyethyl)phenyl] carbamate

9.45 g (0.1 mole) methylchloroformate was added to a solution of 13.72 g (0.1 mole) p-  
aminophenethyl alcohol and 8.4 g (0.1 mole) pyridine in dichloromethane at 0°C. The  
15 reaction was stirred between 0°C and room temperature, and when completed, poured onto  
ice water and the product was extracted with ethyl acetate, dried and the solvent was  
evaporated in vacuo to give 6.7 g (yield 34.7 %) of methyl N-[4-(2-hydroxyethyl)phenyl]  
carbamate.

20 **4-[(Methoxycarbonyl)amino]phenetyl methanesulfonate**

6.0 g (30.7 mmole) methyl N-[4-(2-hydroxyethyl)phenyl] carbamate was dissolved in  
acetonitrile. 6.17 g (61 mmole) triethylamine and 7.0 g (61 mmole) methanesulfonyl  
chloride were added. The mixture was stirred until completion, then the solvent was  
25 evaporated in vacuo, water was added to the residue and the product was extracted with  
dichloromethane to give 7.5 g (yield 89.4 %) of 4-[(methoxycarbonyl)amino]phenetyl  
methanesulfonate.

Methyl N-{4-[2-(4-formylphenoxy)ethyl]phenyl} carbamate

7 g (26 mmole) 4-[(methoxycarbonyl)amino]phenetyl methanesulfonate, 6.2 g (51 mmole) 4-hydroxybenzaldehyde and 7.05 g potassium carbonate in acetonitrile was refluxed for 3 h. The solvent was evaporated in vacuo, 1 M sodium hydroxide was added and the product was extracted with dichloromethane, washed with brine, dried and the solvent was  
5 evaporated. The reaction was not completed and therfor restarted with 3.1 g 4-hydroxybenzaldehyde and 3.5 g potassium carbonate in acetonitrile and refluxed for 4 h. The solvent was evaporated and the residue was stirred in dichloromethane over night. The precipitate was filtered off and the solvent was evaporated to give 5.9 g (yield 75.8 %) of methyl N-{4-[2-(4-formylphenoxy)ethyl]phenyl} carbamate wich was used without  
10 further purification.

5-(4-[2-(4-Methoxycarbonylaminophenyl)ethoxy]benzylidene) thiazolidine-2.4-dione

2 g (6,7 mmole) methyl N-{4-[2-(4-formylphenoxy)ethyl]phenyl} carbamate, 1.57g (13.4  
15 mmole) 2,4-thiazolidinedione, piperidine, acetic acid and toluene were refluxed with water separation in a Dean-Stark apparatus for 3 hours. The formed yellow precipitate was collected by filtration giving 1.9 g (yield 71.2 %) of 5-(4-[2-(4-metoxycarbonylaminophenyl)ethoxy]benzylidene) thiazolidine-2.4-dione.

20 <sup>1</sup>H-NMR (400 MHz; DMSO-d<sub>6</sub>): δ 2.92-2.98 (tr, 2H), 3.63 (s, 3H), 4.16-4.22 (tr, 2H), 7.03-7.08 (d, 2H), 7.17-7.23 (d, 2H), 7.34-7.40 (d, 2H), 7.47-7.53 (d, 2H), 7.21 (s, 1H), 9.54 (s, 1 NH), 12.46 (s, 1 NH).

<sup>13</sup>C-NMR (100 MHz; DMSO-d<sub>6</sub>): δ 34.5, 52.0, 69.0, 115.8, 118.8, 120.7, 125.9, 129.7, 132.3, 132.4, 132.6, 138.0, 154.5, 160.6, 167.9, 168.4.

25

5-([4-[2-(4-Methoxycarbonylaminophenyl) ethoxy]phenyl]methyl) thiazolidine-2.4-dione

1 g (2.5 mmole) 5-(4-[2-(4-methoxycarbonylaminophenyl)ethoxy]benzylidene) thiazolidine-2.4-dione was mixed with Pd/C (5%) and hydrogenated in ethyl acetate for 4  
30 hours at room temperature. The catalyst was filtered off through celite and the solvent was



evaporated in vacuo. All of the starting material was not consumed so the hydrogenation was restarted as above. The catalyst was filtered off through celite and the solvent was evaporated in vacuo. The crude product was purified by crystallization in diethyl ether to give 0.47 g (yield 47 %) of the desired product.

5

<sup>1</sup>H-NMR (400 MHz; DMSO-d<sub>6</sub>): δ 2.89-2.97 (tr, 2H), 2.98-3.08 (m, 1H), 3.23-3.33 (m, 1H), 3.36 (s, 3H), 4.06-4.13 (tr, 2H), 4.80-4.89 (m, 1H), 6.81-6.89 (d, 2H), 7.16-7.24 (d, 2H), 7.33-7.41 (d, 2H), 9.53 (s, 1 NH), 11.97 (s, 1 NH).

<sup>13</sup>C-NMR (100 MHz; DMSO-d<sub>6</sub>): δ 34.8, 36.8, 52.0, 53.5, 68.6, 114.8, 118.7, 129.1, 129.7,  
10 130.8, 132.7, 137.9, 154.5, 158.0, 172.1, 176.2.

#### Example 14.

4-{2-[4-(Hydroxyiminomethyl)phenoxy]ethyl}phenyl methanesulfonate

15 3.52 g (11 mmole) 4-[2-(4-formylphenoxy)ethyl]phenyl methanesulfonate was dissolved in 150 ml ethanol. 2.29 g (33 mmole) hydroxylamine hydrochloride and 3.6 g (44 mmole) sodium acetate in 30 ml water were added. The reaction mixture was stirred at 50°C for 1 h 45 minutes. The solvent was evaporated in vacuo and water was added to give a white precipitate, which was filtered off and washed with hexane to give 3.3 g (yield 89 %) of 4-  
20 {2-[4-(hydroxyiminomethyl)phenoxy]ethyl}phenyl methanesulfonate.

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 3.01-3.12 (tr, 2H), 3.35 (s, 3H), 4.16-4.27 (tr, 2H), 6.9-7.0 (d, 2H), 7.25-7.33 (d, 2H), 7.39-7.54 (m, 4H), 8.04 (s, 1H), 10.92 (s, 1H).

<sup>13</sup>C-NMR (75 MHz; DMSO-d<sub>6</sub>): δ 34.0, 37.2, 67.8, 114.6, 122.0, 125.6, 127.7, 130.5,  
25 132.2, 137.6, 147.5, 159.1.

4-(2-{4-[Hydroxyaminomethyl]phenoxy}ethyl)phenyl methanesulfonate

1.88 g (30 mmole) sodium cyanoborohydride was added to a solution of

2.0 g (6 mmole) 4-{2-[4-(hydroxyiminomethyl)phenoxy]ethyl}phenyl methanesulfonate in 90 ml methanol and 18 ml tetrahydrofuran. Gas evolution was observed. 5 mg methylorange was added resulting in a yellow colour. 4 M hydrochloric acid:dioxan (2:1) was added dropwise until the color was dark red (pH 2-3). The reaction mixture was  
5 poured into water, basified with 2 M sodium hydroxide (pH 9). More water was added and the product was extracted with ethyl acetate, dried, filtered and evaporated. The yellow residue was purified by chromatography on silica gel using ethyl acetate as eluent to give 1.2 g colourless oil of 4-(2-{4-[hydroxyaminomethyl]phenoxy}ethyl)phenyl methanesulfonate.

10

<sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): δ 3.04-3.12 (m, 5H), 3.88 (s, 2H), 4.16-4.21 (tr, 2H), 5.3 (bs, 1H), 6.86-6.90 (m, 2H), 7.18-7.38 (m, 6H).

<sup>13</sup>C-NMR (100 MHz; CDCl<sub>3</sub>): δ 35.1, 37.3, 57.5, 68.3, 114.6, 122.0, 129.3, 130.5, 130.6, 137.9, 147.9, 158.2.

15

2-([4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]phenyl]methyl) 1,2,4-oxadiazolidine-3,5-dione

0.45 g (4 mmole) N-(chlorocarbonyl)isocyanate was added dropwise to a solution of 1.2 g (3.6 ml) 4-(2-{4-[hydroxyaminomethyl]phenoxy}ethyl)phenyl methanesulfonate in 20 ml anhydrous tetrahydrofuran at -5°C and the mixture was stirred at -5°C for 30 minutes. The reaction mixture was poured on to 2 M hydrochloric acid and extracted with ethyl acetate, dried (sodium sulfate), filtered and evaporated in vacuo. The residue was redissolved in ethyl acetate, material that did not go into solution was filtered off. The filtrate was  
25 evaporated in vacuo, diethyl ether was added to give a white precipitate which was filtered off and recrystallized in diethyl ether/acetone to give 0.223 g of the desired product. The mother liquid was evaporated in vacuo and purified by chromatography on silica gel using dichloromethane:methanol (95:5) as eluent and crystallized in diethyl ether to give 0.09 g more of the desired product (yield totally 0.384 g, 26.2 %).

30

<sup>1</sup>H-NMR (500 MHz; DMSO-d<sub>6</sub>): δ 3.04-3.10 (tr, 2H), 3.36 (s, 3H), 4.18-4.24 (tr, 2H), 4.72 (s, 2H), 6.94-6.99 (d, 2H), 7.23-7.32 (m, 4H), 7.42-7.46 (d, 2H), 12.41 (bs, 1H).

<sup>13</sup>C-NMR (125 MHz; DMSO-d<sub>6</sub>): δ 34.4, 37.5, 52.6, 68.0, 114.8, 122.3, 126.1, 130.3, 130.7, 137.9, 147.8, 152.6, 158.2, 158.5.

5

### Example 15.

#### 4-[2-(4-Formylphenoxy)ethyl]phenyl 2-propanesulfonate

3.77 g (13 mmole) 2-propansulfonyl chloride dissolved in dichloromethane was slowly  
10 added to a solution of 3.2 g (13 mmole) 4-[2-(4-hydroxyphenyl)ethoxy]benzaldehyde and  
2.63 g (26 mmole) triethylamine in 80 ml dichloromethane at 0°C. The temperature was  
slowly allowed to raise to room temperature and when the starting material was consumed  
the reaction mixture was poured on to ice. The phases were separated and the organic phase  
15 was washed with sodium carbonate, dried (sodium sulfate), filtered and evaporated. The  
residue was purified by chromatography on silica gel using dichloromethane as eluent to  
give 3.3 g (yield 72.8 %) of 4-[2-(4-formylphenoxy)ethyl]phenyl 2-propanesulfonate.

<sup>1</sup>H-NMR (500 MHz; CDCl<sub>3</sub>): δ 1.57-1.61 (d, 6H), 3.15-3.20 (tr, 2H), 3.46-3.56 (sept, 1H),  
4.26-4.31 (tr, 2H), 7.00-7.05 (m, 2H), 7.25-7.29 (m, 2H), 7.34-7.38 (m, 2H), 7.83-7.88 (m,  
20 2H), 9.92 (s, 1H).

<sup>13</sup>C-NMR (125 MHz; CDCl<sub>3</sub>): δ 16.5, 34.7, 52.2, 68.4, 114.5, 121.9, 129.9, 130.2, 131.8,  
136.6, 147.5, 163.6, 190.5.

#### 5-(4-[2-(4-(2-Propanesulfonyloxy)phenyl)ethoxy]benzylidene) thiazolidine-2,4-dione

25

1.4 g (4 mmole) 4-[2-(4-formylphenoxy)ethyl]phenyl 2-propanesulfonate, 0.94 (8 mmole)  
2,4-thiazolidinedione, 5 drops of piperidine, 6 drops of acetic acid and toluene were  
refluxed with water separation in a Dean-Stark apparatus. When the starting material was  
consumed the heat was removed and the formed crystals were recrystallized in

water:acetone to give 1.5 g (yield 58.6 %) of 5-(4-[2-(4-(2-propanesulfonyloxy)phenyl)ethoxy]benzylidene) thiazolidine-2,4-dione.

<sup>1</sup>H-NMR (500 MHz; DMSO-d<sub>6</sub>): δ 1.40-1.44 (d, 6H), 3.05-3.12 (tr, 2H), 3.65-3.74 (sept, 1H), 4.26-4.32 (tr, 2H), 7.08-7.13 (m, 2H), 7.23-7.28 (m, 2H), 7.41-7.46 (m, 2H), 7.52-7.56 (m, 2H), 7.74 (s, 1H), 12.51 (bs, NH).

<sup>13</sup>C-NMR (125 MHz; DMSO-d<sub>6</sub>): δ 16.5, 34.7, 52.2, 68.4, 114.5, 121.9, 129.9, 130.2, 131.8, 136.6, 147.5, 163.6, 190.5.

10 5-([4-[2-(4-(2-Propanesulfonyloxy)phenyl)ethoxy]phenyl)methyl) thiazolidine-2,4-dione

1.2 g (2.7 mmole) 5-(4-[2-(4-(2-propanesulfonyloxy)phenyl)ethoxy]benzylidene) thiazolidine-2,4-dione was dissolved in 250 ml ethyl acetate by heating. 6 ml acetic acid and 1 g Pd/C (5%) were added and the hydrogenation was started while the solution was warm. After 12 hours at room temperature, more of the catalyst was added. After 60 hours the reaction mixture was filtered through celite and the solvent was evaporated in vacuo. The hydrogenation was restarted with more Pd/C (10 %) and ethyl acetate. After 6 hours the reaction mixture was filtered through celite and the solvent was evaporated in vacuo. The crude product was purified by chromatography on silica gel using dichloromethane:methanol (95:5) as eluent to give 0.557 g (yield 45.9 %) of the desired product.

<sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): δ 1.54-1.58 (d, 6H), 3.06-3.14 (m, 3H), 3.41-3.54 (m, 2H), 4.12-4.19 (tr, 2H), 4.47-4.53 (m, 1H), 6.82-6.87, (m, 2H), 7.11-7.17 (m, 2H), 7.19-7.25 (m, 2H), 7.29-7.35 (m, 2H).

<sup>13</sup>C-NMR (100 MHz; CDCl<sub>3</sub>): δ 16.8, 35.1, 37.8, 52.5, 53.7, 68.3, 114.9, 122.0, 128.0, 130.38, 130.42, 137.3, 148.0, 158.4, 170.3, 174.3.

**Example 16.****4-[Phenylsulfonyl]oxy]phenethyl 1-benzenesulfonate**

42.2 g (240 mmole) benzenesulfonyl chloride in dichloromethane was slowly added to a solution of 15 g (108 mmole) 4-hydroxyphenethyl alcohol and 24.3 g (240 mmole) triethylamine in 120 ml dichloromethane at 0°C. After stirring at 0°C to room temperature the starting material was consumed, water was added, the phases were separated and the organic phase was evaporated in vacuo. Diisopropyl ether was added, two phases were formed, the diisopropyl ether phase was decanted off and the rest of solvent was evaporated to give 32.65 g (yield 73 %) of 4-[phenylsulfonyloxy]phenethyl 1-benzenesulfonate.

<sup>1</sup>H-NMR (300 MHz; CDCl<sub>3</sub>): δ 2.84-2.94 (tr, 2H), 4.12-4.24 (tr, 2H), 6.78-6.88 (m, 2H), 6.96-7.04 (m, 2H), 7.40-7.83 (m, 10H).

**4-[2-(4-Formylphenoxy)ethyl]phenyl 1-benzenesulfonate**

20 g (48 mmole) 4-[phenylsulfonyloxy]phenethyl 1-benzenesulfonate, 11.7 g (95 mmole) p-hydroxybenzaldehyde and 13.27 g (96 mmole) potassium carbonate in 100 ml acetonitrile were refluxed over night. The precipitate was filtered off and the filtrate was evaporated in vacuo. Dichloromethane was added, the solid material was filtered off and the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica gel using ethyl acetate:petroleum ether (1:2) as eluent to give 12 g (yield 65 %) of 4-[2-(4-formylphenoxy)ethyl]phenyl 1-benzenesulfonate.

<sup>1</sup>H-NMR (500 MHz; CDCl<sub>3</sub>): δ 3.05-3.10 (tr, 2H), 4.18-4.24 (tr, 2H), 6.90-6.98 (m, 4H), 7.18-7.23 (m, 2H), 7.43-7.54 (m, 2H), 7.63-7.69 (m, 1H), 7.78-7.84 (m, 4H), 9.86 (s, 1H).

<sup>13</sup>C-NMR (125 MHz; CDCl<sub>3</sub>): δ 34.6, 68.2, 114.5, 122.1, 128.1, 128.9, 129.8, 129.9, 131.7, 134.0, 135.1, 136.9, 148.0, 163.4, 190.5.

5-(4-[2-(4-(Benzenesulfonyloxy)phenyl)ethoxy]benzylidene) thiazolidine-2.4-dione

2.0 g (5.2 mmole) 4-[2-(4-formylphenoxy)ethyl]phenyl 1-benzenesulfonate, 1.53 g (13 mmole) 2.4-thiazolidinedione, 5 drops of piperidine and 6 drops of acetic acid in toluene were refluxed with water separation in a Dean-Stark apparatus. When the reaction mixture was cooled to room temperature a precipitate was formed and filtered off to give 1.5 g (yield 60 %) of 5-(4-[2-(4-(benzenesulfonyloxy)phenyl)ethoxy]benzylidene) thiazolidine-2.4-dione.

<sup>1</sup>H-NMR (500 MHz; DMSO-d<sub>6</sub>): δ 2.99-3.07 (tr, 2H), 4.21-4.28 (tr, 2H), 6.93-6.99 (m, 2H), 7.05-7.10 (m, 2H), 7.30-7.36 (m, 2H), 7.50-7.55 (m, 2H), 7.63-7.70 (m, 2H), 7.73 (s, 1H), 7.78-7.9 (m, 3H), 12.5 (s, NH).

<sup>13</sup>C-NMR (125 MHz; DMSO-d<sub>6</sub>): δ 34.1, 68.2, 115.6, 120.5, 122.0, 125.8, 128.3, 130.0, 130.7, 132.0, 132.3, 134.6, 135.2, 137.8, 147.7, 160.2, 167.6, 168.1.

5-([4-[2-(4-(Benzenesulfonyloxy)phenyl)ethoxy]phenyl]methyl) thiazolidine-2.4-dione

1.5 g (3.1 mmole) 5-(4-[2-(4-(benzenesulfonyloxy)phenyl)ethoxy]benzylidene) thiazolidine-2.4-dione was hydrogenated on 1 g Pd/C (5%) in ethyl acetate and acetic acid (2.5 %) at atmospheric pressure for 24 hours. The reaction mixture was filtered through celite and the solvent was evaporated in vacuo. The starting material was not completely consumed, therefor the hydrogenation was restarted twice with Pd/C (10%), followed by purification by chromatography on silica gel using dichloromethane:methanol (95:5) as eluent to give 0.728 g (yield 48.6 %) of the desired product.

<sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): δ 3.01-3.14 (m, 3H), 3.40-3.49 (dd, 1H), 4.09-4.15 (tr, 2H), 4.47-4.53 (dd, 1H), 6.78-6.86 (d, 2H), 6.89-6.96 (d, 2H), 7.10-7.16 (m, 2H), 7.17-7.23 (d, 2H), 7.49-7.57 (tr, 2H), 7.63-7.71 (tr, 1H), 7.81-7.88 (d, 2H).

<sup>13</sup>C-NMR (125 MHz; CDCl<sub>3</sub>): δ 34.8, 37.5, 53.5, 68.0, 114.6, 122.0, 127.7, 128.2, 128.9, 129.9, 130.1, 134.0, 135.2, 137.3, 147.9, 157.9, 170.8, 174.5.

**Example 17.****2-[4-(Methylmercapto)phenyl]-1-ethanol**

5 5.5 ml 1 M borane-tetrahydrofuran complex was slowly added to a solution of 1 g (5.5 mmole) 4-(methylmercapto)phenyl acetic acid in 5 ml tetrahydrofuran at -10°C. The reaction mixture was allowed to reach room temperature and the reaction was followed by TLC. After completion 10 ml methanol was added and the solvents were evaporated. Diethyl ether and 2 M sodium hydroxide was added, the phases were separated, the organic  
10 phase was dried, filtered and evaporated in vacuo to give 0.8 g (yield 84.4 %) of 2-[4-(methylmercapto)phenyl]-1-ethanol.

<sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): δ 2.46 (s, 3H), 2.77-2.83 (tr, 2H), 3.74-3.82 (qvar, 2H), 7.12-7.17 (m, 2H), 7.20-7.24 (m, 2H).

15 <sup>13</sup>C-NMR (100 MHz; CDCl<sub>3</sub>): δ 16.2, 38.6, 63.5, 127.2, 129.6, 137.7, 136.2.

**4-[2-(4-Methylmercaptophenyl)ethoxy]benzaldehyd**

1.7 g (10 mmole) 2-[4-(methylsulfanyl)phenyl]-1-ethanol, 5.24 g (20 mmole)  
20 triphenylphosphine and 5.05 g (20 mmole) 1,1-(azodicarbonyl)dipiperidine was added to a mixture of 2.47 g (20 mmole) 4-hydroxybenzaldehyde in 40 ml dichloromethane under argon atmosphere. Stirring at room temperature for 2 hours, (more dichloromethane was added after 20 minutes), gave a solid material that was removed by filtration. The filtrate was purified by chromatography on silica gel using dichloromethane as eluent to give 2.3 g  
25 (yield 84.4 %) of 4-[2-(4-methylmercaptophenyl)ethoxy]benzaldehyd.

<sup>13</sup>C-NMR (100 MHz; CDCl<sub>3</sub>): δ 16.1, 35.1, 68.9, 114.8, 127.1, 129.5, 130.1, 132.0, 134.7, 136.7, 163.8, 190.7.

30 5-(4-[2-(4-Methylmercaptophenyl)ethoxy]benzylidene) thiazolidine-2,4-dione

1 g (3.7 mmole) 4-[2-(4-Methylmercaptophenyl)ethoxy]benzaldehyd, 1.09 (9.25 mmole) 2.4-thiazolidinedione, 5 drops of piperidine, 6 drops of acetic acid and toluene were refluxed with water separation in a Dean-Stark apparatus for 1 hour. The heat was removed and the crystals were recrystallized in dichloromethane:methanol (95:5) to give 1.1 g (yield 80 %) of 5-(4-[2-(4-methylmercaptophenyl)ethoxy]benzylidene) thiazolidine-2.4-dione.

<sup>1</sup>H-NMR (500 MHz; DMSO-d<sub>6</sub>): δ 2.46 (s, 3H), 3.0-3.05 (tr, 2H), 4.22-4.38 (tr, 2H), 7.08-7.12 (m, 2H), 7.21-7.24 (m, 2H), 7.27-7.31 (m, 2H), 7.53-7.57 (m, 2H), 7.75 (s, 1H), 12.54 (bs, 1H).

<sup>13</sup>C-NMR (125 MHz; DMSO-d<sub>6</sub>): δ 15.2, 34.4, 68.6, 115.6, 120.5, 125.7, 126.4, 129.8, 132.0, 132.3, 135.1, 136.0, 160.3, 167.7, 168.2.

5-([4-[2-(4-Methylmercaptophenyl)ethoxy]phenyl]methyl) thiazolidine-2.4-dione

15

1 g (2.7 mmole) 5-(4-[2-(4-methylmercaptophenyl)ethoxy]benzylidene) thiazolidine-2.4-dione and 1.36 g (5.4 mmole) diethyl-1.4-dihydro-2.6-dimethyl-3.5-pyridinedicarboxylate were mixed and heated to 160° C under vacuum (when it melted), after 1 hour at this temperature the heat was removed. Toluene was added, crystals of the starting material was removed by filtration, the filtrate was evaporated and purified by chromatography on silica gel twice using first dichloromethane:methanol (98:2) and then diisopropyl ether as eluents. The reaction was restarted with unreacted material and 0.4 g diethyl-1.4-dihydro-2.6-dimethyl-3.5-pyridinedicarboxylate and kept at 160°C for 2 hours. The product was boiled in diisopropyl ether, and purified by chromatography on silica gel using diisopropyl ether as eluent. The combined fractions gave 0.346 g (yield 36 %) of the desired product.

25

<sup>1</sup>H-NMR (500 MHz; CDCl<sub>3</sub>): δ 2.53 (s, 3H), 3.08-3.18 (m, 3H), 3.46-3.54 (dd, 1H), 4.16-4.22 (tr, 2H), 4.52-4.58 (dd, 1H), 6.87-6.92 (m, 2H), 7.16-7.20 (m, 2H), 7.25-7.30 (m, 4H).



<sup>13</sup>C-NMR (125 MHz; CDCl<sub>3</sub>): δ 15.9, 35.0, 37.5, 53.5, 68.4, 114.6, 126.8, 129.3, 130.1, 127.5, 135.1, 136.2, 158.1, 170.3, 174.4.

**Example 18.**

5    2-[4-(Methylsulfonyl)phenyl]-1-ethanol

10 g (47 mmole) 4-(methylsulfonyl)phenyl acetic acid was dissolved in 40 ml tetrahydrofuran and the solution was cooled to -10°C. At this temperature 4-(methylsulfonyl)phenyl acetic acid precipitates. 47 ml 1 M borane-tetrahydrofuran  
10 complex was added slowly. The reaction mixture was allowed to reach room temperature and the reaction was followed by TLC. After completion 100 ml methanol was added and the solvents were evaporated. The residue was dissolved in dichloromethane and washed with sodium hydroxide. The organic phase was dried, filtered and evaporated in vacuo to give 7.5 g (yield 79.7 %) of 2-[4-(methylsulfonyl)phenyl]-1-ethanol.

15

<sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): δ 1.73 (m, 1H), δ 2.96 (tr, 2H), 3.05 (s, 3H), 3.91 (q, 2H), 7.45 (m, 2H), 7.87 (m, 2H).

4-[2-(4-Formylphenoxy)ethyl]phenyl methyl sulfone

20

1.83 g (15 mmole) 4-hydroxybenzaldehyde was dissolved in 35 ml dichloromethane under argon atmosphere. 1.5 g (7.5 mmole) 2-[4-(methylsulfonyl)phenyl]-1-ethanol was added followed by 3.93 g (15 mmole) triphenylphosphine and 3.78 g (15 mmole) 1,1-(azodicarbonyl)dipiperidine. The reaction mixture was stirred at room temperature and  
25 after 2 hours a precipitate is observed. The reaction was disrupted after 5 hours and the reaction mixture was filtered. The filtrate was purified by chromatography on silica gel using dichloromethane:methanol (98:2) as eluent giving 1.66 g (yield 54.5%) of 4-[2-(4-formylphenoxy)ethyl]phenyl methyl sulfone.

<sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): δ 3.04 (s, 3H), 3.22 (tr, 2H), 4.30 (tr, 2H), 6.96-7.00 (m, 2H), 7.48-7.52 (m, 42H), 7.80-7.85 (m, 2H), 7.88-7.91 (m, 2H), 9.87 (s, 1H)

5-(4-[2-(4-Methanesulfonylphenyl)ethoxy]benzylidene) thiazolidine-2,4-dione

5

1 g (3.3 mmole) 4-[2-(4-formylphenoxy)ethyl]phenyl methyl sulfone, 0.96 g (8.2 mmole) 2,4-thiazolidinedione, 5 drops of piperidine, 6 drops of acetic acid and toluene were refluxed with water separation in a Dean-Stark apparatus for 1 hour. The heat was removed and the yellow precipitate was filtered off. A slurry of the precipitate and  
10 dichloromethane:methanol (95:5) was refluxed. The product was collected by filtration giving 0.9 g (yield 67.6 %) of 5-(4-[2-(4-methanesulfonylphenyl)ethoxy]benzylidene) thiazolidine-2,4-dione.

<sup>1</sup>H-NMR (500 MHz; DMSO-d<sub>6</sub>): δ 3.13-3.18 (m, 5H), 4.31 (tr, 2H), 7.06-7.10 (m, 2H),  
15 7.50-7.54 (m, 2H), 7.72 (s, 1H), 7.57-7.61 (m, 2H), 7.82-7.87 (m, 2H), 12.50 (bs, 1H).  
<sup>13</sup>C-NMR (125 MHz; DMSO-d<sub>6</sub>): δ 35.0, 44.1, 68.2, 115.9, 121.0, 126.2, 127.4, 130.4, 132.1, 132.5, 139.5, 145.0, 160.5, 168.0, 168.4.

5-([4-[2-(4-Methanesulfonylphenyl)ethoxy]phenyl]methyl) thiazolidine-2,4-dione

20

0.9 g (2.2 mmole) 5-(4-[2-(4-methanesulfonylphenyl)ethoxy]benzylidene) thiazolidine-2,4-dione was dissolved in approximately 550 ml ethyl acetate/acetic acid (0.9%) under heating. Pd/C (10%) was added as catalyst to the warm solution followed by hydrogenation for 17 hours. The reaction mixture was filtered through celite and the solvent was  
25 evaporated in vacuo.

The yellow residue was refluxed in dichloromethane. The solid material was filtered off and purified by flash chromatography using dichloromethane:methanol (95:5). The product still contained some unreacted starting material and it was therefore hydrogenated once more with Pd/C (10%) in ethyl acetate. Filtration through celite gave 0.25 g (yield 28%) of  
30 the desired product.

<sup>1</sup>H-NMR (500 MHz; CDCl<sub>3</sub>): δ 3.0-3.1 (m, 6H), 3.15 (tr, 2H), 4.35-4.45 (dd, 1H), 4.2 (tr, 2H), 4.42-4.5 (dd, 1H), 6.8 (d, 2H), 7.15 (d, 2H), 7.5 (d, 4H), 7.85 (d, 2H).

5 <sup>13</sup>C-NMR (125 MHz; CDCl<sub>3</sub>): δ 35.6, 37.6, 44.5, 53.7, 67.7, 114.8, 127.5, 128.1, 130.0, 130.4, 138.6, 135.1, 157.9, 170.9, 174.7.

#### Example 19.

##### 3-Methoxy-4-(methylsulfonyloxy)phenethyl methanesulfonate

10

44 g (0.39 mole) methanesulfonyl chloride was slowly added to a solution of 30 g (0.178 mole) homovanillyl alcohol and 45.3 g (0.45 mmole) triethylamine in 500 ml dichloromethane at - 10°C. After stirring at room temperature over night the salts were filtered off, the organic phase was washed with sodium bicarbonate and brine, dried  
15 (magnesium sulphate) and evaporated in vacuo to give 50 g (yield 86 %) of 3-methoxy-4-(methylsulfonyloxy)phenethyl methanesulfonate.

##### 4-[2-(4-Formylphenoxy)ethyl]-2-methoxyphenyl methanesulfonate

20 50 g (0.154 mole) 3-methoxy-4-(methylsulfonyloxy)phenethyl methanesulfonate, 48.8 g (0.4 mole) p-hydroxybenzaldehyde, 65.45 g (0.473 mole) potassium carbonate in 500 ml acetonitrile was refluxed for 4 hours. The precipitate was filtered off and the solvent was evaporated. Dichloromethane was added and the organic phase was washed with water, dried (magnesium sulphate), filtered and the solvent was evaporated to give 34 g (yield 63  
25 %) of 4-[2-(4-formylphenoxy)ethyl]-2-methoxyphenyl methanesulfonate.

##### 5-(4-[2-(3-Methoxy-4-methanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2,4-dione

34 g (97 mmole) 4-[2-(4-formylphenoxy)ethyl]-2-methoxyphenyl methanesulfonate, 12.5 g (107 mmole) 2,4-thiazolidinedione, 0.5 ml piperidine and 0.5 ml acetic acid in 500 ml toluene was refluxed with water separation in a Dean-Stark apparatus for 4 hours. The solvent was evaporated, acetic acid was added and the mixture was heated. The formed precipitate was filtered and washed with diethylether to give 31.5 g (yield 72 %) of 5-(4-[2-(3-methoxy-4-methanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2,4-dione.

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 3.0-3.12 (t, 2H), 3.3 (s, 3H), 3.85 (s, 3H), 4.22-4.35 (t, 2H), 6.9-7.0 (d, 1H), 7.05-7.15 (m, 2H), 7.15-7.27 (d, 2H), 7.5-7.6 (d, 2H), 7.75 (s, 1H).

5-([4-[2-(3-Methoxy-4-methanesulfonyloxyphenyl)ethoxy]phenyl]methyl) thiazolidine-2,4-dione

1.5 g (33.4 mmole) 5-(4-[2-(3-methoxy-4-methanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2,4-dione was hydrogenated on Pd/C (10%) in 150 ml ethyl acetate and 5 ml acetic acid at atmospheric pressure over night. The catalyst was filtered off and the solvent was evaporated in vacuo. The residue was crystallized in ethanol to give 1.1 g (yield 73 %) of the desired product.

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 2.97-3.15 (m, 3H), 3.25-3.4 (m and s, 4H), 3.85 (s, 3H), 4.15-4.25 (m, 2H), 4.77-4.9 (m, 1H), 6.82-7.0 (m, 3H), 7.1-7.3 (m, 4H)

<sup>13</sup>C-NMR (75 MHz; DMSO-d<sub>6</sub>): δ 34.7, 36.2, 38.1, 53.0, 55.7, 67.6, 114.1, 114.2, 121.0, 123.5, 128.6, 130.3, 136.3, 138.9, 151.0, 157.3, 171.7, 175.8.

## Example 20

3-(Methylsulfonyloxy)phenethyl methanesulfonate

9.09 g (79.6 mmole) methanesulfonyl chloride was slowly added to a solution of 5 g (36.2 mmole) 3-hydroxyphenethyl alcohol and 9.14 g (90.5 mmole) triethylamine in 150 ml dichloromethane at 0°C. After stirring at room temperature over night the salts were

filtered off, the organic phase was washed with sodium bicarbonate and brine, dried (magnesium sulfate) and evaporated in vacuo to give 9.3 g (yield 87 %) of 3-(methylsulfonyloxy)phenethyl methanesulfonate.

5 3-[2-(4-Formylphenoxy)ethyl]phenyl methanesulfonate

9.3 g (31.6 mmole) 3-(methylsulfonyloxy)phenethyl methanesulfonate, 9.91 g (82 mmole) p-hydroxybenzaldehyde and 13 g (94,8 mmole) potassium carbonate in 200 ml acetonitrile were refluxed for 4 hours. The precipitate was filtered off and the solvent was evaporated  
10 in vacuo. Dichloromethane was added and the organic phase was washed with water, dried (magnesium sulfate), filtered and the solvent was evaporated to give 8.72 g (yield 88 %) of 3-[2-(4-formylphenoxy)ethyl]phenyl methanesulfonate.

15 5-(4-[2-(3-Methanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2.4-dione

5.31 g (16.6 mmole) 3-[2-(4-formylphenoxy)ethyl]phenyl methanesulfonate, 2.13 g (18.2 mmole) 2.4-thiazolidinedione, 0.5 ml piperidine and 0.5 ml acetic acid in 300 ml toluene were refluxed with water separation in a Dean-Stark apparatus for 4 hours. The solvent was evaporated, acetic acid was added and the mixture was heated. The formed precipitate was  
20 filtered off and washed with diethyl ether to give 3.6 g (yield 51 %) of 5-(4-[2-(3-methanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2.4-dione.

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 3.05-3.17 (tr, 2H), 3.37 (s, 3H), 4.25-4.35 (tr, 2H), 7.05-7.13 (d, 2H), 7.17-7.26 (d, 1H), 7.3-7.4 (m, 2H), 7.4-7.48 (m, 1H), 7.49-7.59 (d, 2H),  
25 7.75 (s, 1H).

<sup>13</sup>C-NMR (75 MHz; DMSO-d<sub>6</sub>): δ 34.2, 37.3, 67.9, 115.3, 120.1, 120.2, 122.6, 125.5, 127.9, 129.8, 131.7, 132.0, 140.7, 149.0, 166.0, 167.3, 167.8.

30 5-([4-[2-(3-Methanesulfonyloxyphenyl)ethoxy]phenyl]methyl) thiazolidine-2.4-dione

2 g (84 mmole) 5-(4-[2-(3-methanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2,4-dione was hydrogenated in 200 ml ethylacetate and 10 ml acetic acid in the presence of Pd/C (10%) at atmospheric pressure over night. The catalyst was filtered off and the solvent was evaporated in vacuo. The residue was crystallized in ethanol to give 1.18 g (yield 59 %) of the desired product.

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 3.0-3.15 (m, 3H), 3.25-3.45 (m, 4H); 4.1-4.25 (d, 2H), 4.8-4.9 (m, 1H), 6.8-6.95 (d, 2H), 7.1-7.2 (d, 2H), 7.2-7.3 (d, 1H), 7.3-7.5 (m, 3H).

<sup>13</sup>C-NMR (75 MHz; DMSO-d<sub>6</sub>): δ 34.4, 36.2, 37.2, 53.0, 67.5, 114.3, 120.0, 122.6, 127.9, 128.6, 129.8, 130.3, 141.0, 149.0, 157.3, 171.8, 175.8.

#### Example 21.

##### 4-(Trifluoromethylsulfonyloxy)phenethyl trifluoromethansulfonate

10.3 g (75 mmole) p-hydroxyphenethyl alcohol was dissolved in dichloromethane. 37 g (0.18 mole) 2,6-di-tertbutyl-4-methylpyridine was added followed by slow addition of a solution of 48.5 g (0.172 mole) trifluoroacetic anhydride in dichloromethane at 0°C. The reaction was allowed to reach room temperature and stirred for 48 hours. The reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica gel using dichloromethane as eluent to give 20 g (yield 76.2 %) of 4-(trifluoromethylsulfonyloxy)phenethyl trifluoromethansulfonate.

##### 4-[2-(4-Formylphenoxy)ethyl]phenyl trifluoromethanesulfonate

A mixture of 0.85 g (2.11 mmole) of 4-(trifluoromethylsulfonyloxy)phenethyl trifluoromethansulfonate, 0.27 g (2.2 mmole) p-hydroxybenzaldehyde and 0.72 g (2.2 mmole) cesium carbonate in acetonitrile was stirred at room temperature over night. The salts were filtered off and the solvent evaporated in vacuo. Purification by chromatography

on silica gel using dichloromethane as eluent gave 0.6 g (yield 75 %) of 4-[2-(4-formylphenoxy)ethyl]phenyl trifluoromethanesulfonate.

5 5-(4-[2-(4-Trifluoromethanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2.4-dione

7 g (18.7 mmole) of 4-[2-(4-formylphenoxy)ethyl]phenyl trifluoromethanesulfonate, 2.74 g (23.4 mmole) 2.4-thiazolidinedione and 3.8 g (46.8 mmole) sodium acetate were mixed and heated under vacuum to 140°C when it melted. It was kept at 140° C for 20 minutes  
10 and thereafter taken off the heat, water:acetone (2:1) was added, the formed crystals were filtered off and recrystallization in dichloromethane gave 2.09 g (yield 24 %) 5-(4-[2-(4-trifluoromethanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2.4-dione.

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 3.02-3.12 (tr, 2H), 4.2-4.35 (tr, 2H), 7.0-7.1 (m, 2H),  
15 7.35-7.45 (m, 2H), 7.45-7.56 (m, 4H), 7.75 (s, 1H).

<sup>13</sup>C-NMR (75 MHz; DMSO-d<sub>6</sub>): δ 34.2, 68.1, 115.6, 120.5, 121.4, 125.8, 128(q, J=8), 131.4, 132.0, 132.3, 139.6, 148.1, 160.2, 167.6, 168.2.

20 5-([4-[2-(4-Trifluoromethanesulfonyloxyphenyl)ethoxy]phenyl]methyl) thiazolidine-2.4-dione

2 g (4.22 mmole) 5-(4-[2-(4-trifluoromethanesulfonyloxyphenyl)ethoxy]benzylidene) thiazolidine-2.4-dione and 2.14 g (8.44 mmole) diethyl-1.4-dihydro-2.6-dimethyl-3.5-  
25 pyridine dicarboxylate were mixed and heated to 180°C under vacuum when it melted, the temperature raised to 230° C and after 30 minutes the heat was removed. Purification by chromatography on silica gel with heptan/ethylacetate as eluent gave 0.768 g (yield 38 %) of the desired product.

<sup>1</sup>H-NMR (300 MHz; DMSO-d<sub>6</sub>): δ 2.95-3.45 (m, 3H), 4.05-4.25 (m, 2H), 4.8-4.9 (m, 1H), 6.8-6.95 (m, 2H), 7.05-7.20 (m, 2H), 7.35-7.47 (m, 2H), 7.47-7.6 (m, 2H).

5 Biological activity

The biological activity of the compounds was tested in obese diabetic mice of the Umeå ob/ob strain. Groups of mice received the test compound by gavage once daily for 7 days. On the last day of the experiment the animals were anesthetized 2h after dose in a non-fed  
10 state and blood was collected from an incised artery. Plasma was analyzed for concentration of glucose, insulin and triglycerides. A group of untreated obese diabetic mice of the same age served as control. The individual values for glucose, insulin and triglyceride levels of the mice from the test group were expressed as the percent rage of the corresponding values from the control group.

15 The desired "therapeutic effect" was calculated as the average percent reduction of the three variables glucose, insulin and triglycerides below the levels in the control animals. The therapeutic effect of the tested compounds according to the invention was compared to the same effect in the prior art compound troglitazone, administrered by gavage in the oral dose of 300 µmol/kg for 7 days.

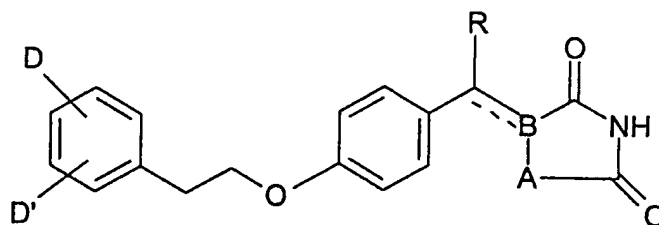
20

The superior effects of the tested compounds according to the invention compared to that of troglitazone when given in the same oral dose demonstrate the increased potency and efficiacy of the claimed compounds.



CLAIMS

1. A compound having the general formula I



and stereo and optical isomers and racemates thereof as well as pharmaceutically  
 10 acceptable salts, solvates and hydrates thereof, in which formula

== is a singel or double bond,

R is H or alkyl,

A is S, O or NH,

15 B is C, CH or N,

D is situated in the orto, meta or para position and is representing CN or -X-Y-Z,

D' is situated in the orto, meta or para position and is representing H, -O-alkyl, alkyl,  
 halogen or -X-Y-Z, wherein

X is O, NR<sup>1</sup>, SO<sub>2</sub> or S and R<sup>1</sup> is H or alkyl,

20 Y is SO<sub>2</sub>, CO or a chemical bond,

Z is alkyl, alkyl substituted by one or more fluoro or chloro atoms, aryl, substituted aryl,  
 alkylaryl, OR<sup>2</sup> or NHR<sup>3</sup>, wherein

R<sup>2</sup> is alkyl, aryl, alkylaryl, substituted aryl or substituted alkyl,

R<sup>3</sup> is H, alkyl, aryl, alkylaryl, substituted aryl or substituted alkyl,

25 provided that

- when X is O or  $\text{NR}^1$ , then Y is either  $\text{SO}_2$  or CO and Z is, when Y is a)  $\text{SO}_2$ , selected from the group consisting of alkyl, alkyl substituted by one or more fluoro or chloro atoms, aryl, substituted aryl and alkylaryl, when Y is b) CO, selected from the group consisting of  $\text{OR}^2$  and  $\text{NHR}^3$  wherein  $\text{R}^2$  and  $\text{R}^3$  are as defined above,
- 5 when X is  $\text{SO}_2$ , then Y is a chemical bond and Z is selected from the group consisting of alkyl, alkyl substituted by one or more fluoro or chloro atoms, aryl, substituted aryl, alkylaryl and  $\text{OR}^2$ , wherein  $\text{R}^2$  is as defined above,
- when X is S, then Y is a chemical bond and Z is selected from the group consisting of alkyl, alkyl substituted by one or more fluoro or chloro atoms, aryl, substituted
- 10 aryl alkylaryl,
- and further provided that when B is N, A is O.

2. A compound according to claim 1, wherein

==== is a single or double bond,

15 R is a H or alkyl,

A is S or O,

B is C, CH or N,

D is situated in the orto, meta or para position and is representing -X - Y - Z

D' is situated in the orto, meta or para position and is representing

20 H, -O-alkyl or -X - Y - Z,

X is O,  $\text{NR}^1$ ,  $\text{SO}_2$ , or S wherein  $\text{R}^1$  is H or alkyl,

Y is  $\text{SO}_2$ , CO or a chemical bond,

Z is alkyl, aryl, alkylaryl, substituted aryl,  $\text{CF}_3$ ,  $\text{OR}^2$  and  $\text{NHR}^3$ , wherein  $\text{R}^2$  and  $\text{R}^3$  are as defined in claim 1,

25 provided that

when X is O or  $\text{NR}^1$ , then Y is either  $\text{SO}_2$  or CO and Z is, when Y is a)  $\text{SO}_2$ , selected from the group consisting of alkyl,  $\text{CF}_3$ , aryl, substituted aryl and alkylaryl, when Y is b) CO, selected from the group consisting of  $\text{OR}^2$  and  $\text{NHR}^3$  wherein  $\text{R}^2$  and  $\text{R}^3$  are as defined above,

when X is SO<sub>2</sub>, then Y is a chemical bond and Z is selected from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl, alkylaryl and OR<sup>2</sup>, wherein R<sup>2</sup> is as defined above,

when X is S, then Y is a chemical bond and Z is selected from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl and alkylaryl,  
 5 and further provided that when B is N, A is O.

3. A compound according to any of the preceeding claims wherein

10  $\equiv$  is a single or double bond,

R is H,

A is S,

B is C or CH,

D is situated in the orto, meta or para position and is representing - X - Y - Z,

15 D' is H,

X is O, NR<sup>1</sup>, SO<sub>2</sub>, or S wherein R<sup>1</sup> is H or alkyl,

Y is SO<sub>2</sub>, CO or a chemical bond,

Z is alkyl, aryl, alkylaryl, substituted aryl, CF<sub>3</sub>, OR<sup>2</sup> or NHR<sup>3</sup>, wherein R<sup>2</sup>, and R<sup>3</sup> are as defined in claim 1,

20 provided that

when X is O or NR<sup>1</sup>, then Y is either SO<sub>2</sub> or CO and Z is, when Y is a) SO<sub>2</sub>, selected from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl and alkylaryl, when Y is b) CO, selected from the group consisting of OR<sup>2</sup> and NHR<sup>3</sup> wherein R<sup>2</sup> and R<sup>3</sup> are as defined above,

25 when X is SO<sub>2</sub>, then Y is a chemical bond and Z is selected from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl, alkylaryl and OR<sup>2</sup>, wherein R<sup>2</sup> is as defined above,

when X is S, then Y is a chemical bond and Z is selected from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl and alkylaryl.

4. A compound according to any of the preceeding claims wherein

==== is a single bond or double bond,

R is H,

5 A is S,

B is C or CH,

D is situated in the orto, meta or para position and is representing - X - Y - Z,

D' is H,

X is O, NH, SO<sub>2</sub> or S,

10 Y is SO<sub>2</sub>, CO or a chemical bond,

Z is alkyl, aryl, alkylaryl, substituted aryl, CF<sub>3</sub>, OR<sup>2</sup> or NHR<sup>3</sup>, wherein R<sup>2</sup> and R<sup>3</sup> are as defined in claim 1,

provided that

15 when X is O or NR<sup>1</sup>, then Y is either SO<sub>2</sub> or CO and Z is, when Y is a) SO<sub>2</sub>, selected from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl and alkylaryl, when Y is b) CO, selected from the group consisting of OR<sup>2</sup> and NHR<sup>3</sup>, wherein R<sup>2</sup> and R<sup>3</sup> are as defined above,

when X is SO<sub>2</sub>, then Y is a chemical bond and Z is selected from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl, alkylaryl and OR<sup>2</sup>, wherein R<sup>2</sup> is as defined  
20 above,

when X is S, then Y is a chemical bond and Z is selected from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl and alkylaryl.

25 5. A compound according to any of the preceeding claims wherein D is situated in the para position.

6. A compound according to any of the preceeding claims wherein

==== is a single bond,

R is H,

A is S,

B is CH,

D is situated in the para position and is representing - X - Y - Z,

5 D' is H,

X is O or NH,

Y is SO<sub>2</sub> or CO,

Z is alkyl, aryl, alkylaryl, substituted aryl, CF<sub>3</sub>, OR<sup>2</sup> and NHR<sup>3</sup>, wherein R<sup>2</sup> and R<sup>3</sup> are as defined in claim 1,

10 provided that

when X is O or NR<sup>1</sup>, then Y is either SO<sub>2</sub> or CO and Z is, when Y is a) SO<sub>2</sub>, selected from the group consisting of alkyl, CF<sub>3</sub>, aryl, substituted aryl and alkylaryl, when Y is b) CO, selected from the group consisting of OR<sup>2</sup> and NHR<sup>3</sup> wherein R<sup>2</sup> and R<sup>3</sup> are as defined above.

15

7. A compound according to any of the preceeding claims wherein

==== is a single bond,

R is H,

A is S,

20 B is CH,

D is situated in the para position and is representing - X - Y - Z,

D' is H,

X is O or NH,

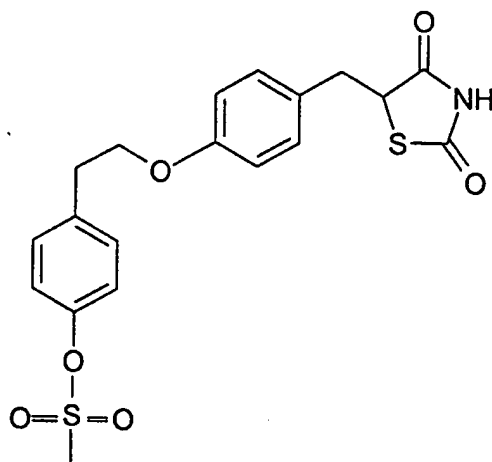
Y is SO<sub>2</sub> or CO,

25 Z is alkyl, NHR<sup>3</sup> or OR<sup>2</sup>, wherein R<sup>2</sup> is alkyl and R<sup>3</sup> is alkyl,

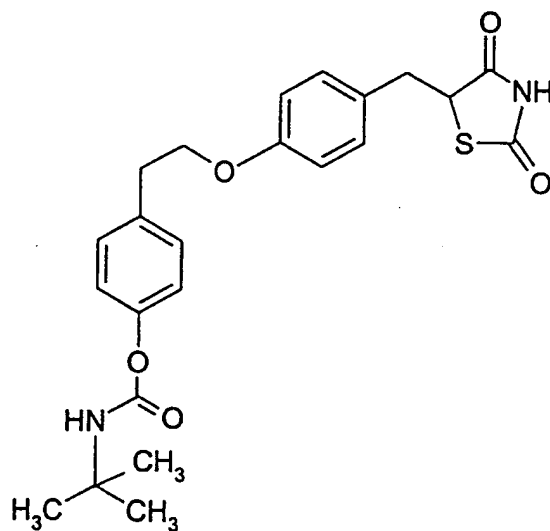
provided that

when X is O or NR<sup>1</sup>, then Y is either SO<sub>2</sub> or CO and Z is, when Y is a) SO<sub>2</sub>, selected from the group consisting of alkyl, CF<sub>3</sub>, when Y is b) CO, selected from the group consisting of OR<sup>2</sup> and NHR<sup>3</sup> wherein R<sup>2</sup> and R<sup>3</sup> are as defined above.

8. A compound according to any of the preceding claims having the formula

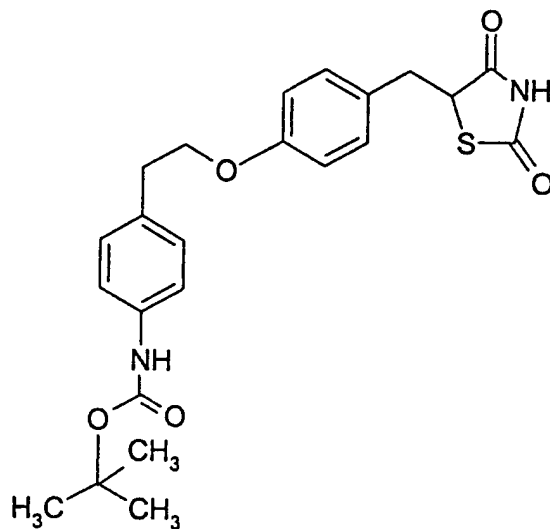


5 or

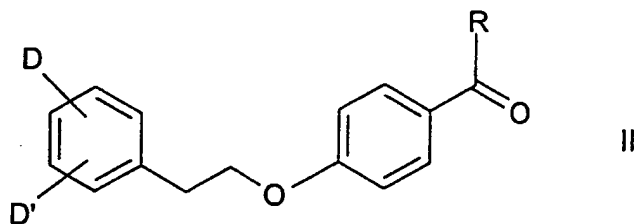


or

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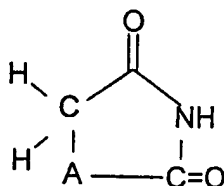


9. A process for preparing a compound according to claim 1, characterized by  
a) condensating a carbonyl compound of the formula II

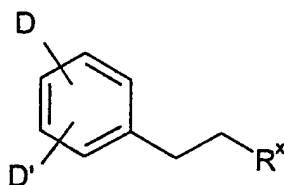


with a compound of the formula

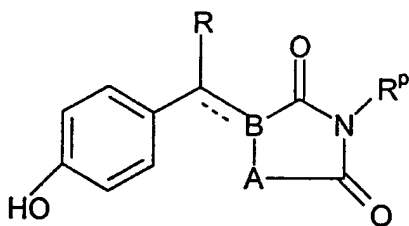
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- and if desired, followed by reduction of the obtained compound, to the formation of a  
 5 compound of the formula I, wherein A is S and B is C or CH, or  
 b) reacting a compound of the formula



- 10 with a compound of the formula



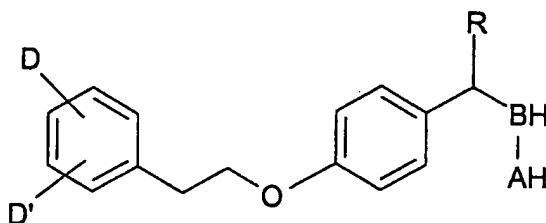
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wherein D, D', R, A and B are as defined above, R<sup>x</sup> is a leaving group or a hydroxyl group  
 and R<sup>p</sup> is hydrogen or a protecting group, followed, if necessary, by removal of the  
 protecting group to the formation of a compound of the formula I, or

20

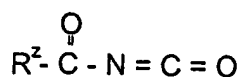
- c) reacting a compound of the formula





with a compound of the formula

5



wherein D, D', R, A and B are as defined above, and R<sup>Z</sup> is a halogen, to the formation of a  
 10 compound of the formula I wherein A is O, B is N and  $\equiv$  is a single bond,  
 whereafter, if desired, the compound obtained according to any of methods a) - c) is  
 converted to a stereoisomer and/or a pharmaceutically acceptable salt thereof.

10. A process according to claim 9, characterized by the preparation of a compound  
 15 according to any of claims 2-8.

11. A compound according to any of claims 1-8 for use in therapy.

12. A pharmaceutical formulation containing a compound according to any of claims 1-8  
 20 as active ingredient optionally together with an acceptable carrier.

13. The use of a compound according to any of claims 1-8 in the manufacture of a  
 formulation for the treatment of clinical conditions associated with the insulin  
 resistance syndrom.

25

14. A method for the treatment of clinical conditions associated with the insulin resistance wherein a therapeutically active amount of a compound according to any of claims 1-8 administered to a mammal in the need of such treatment.
- 5 15. A pharmaceutical formulation for use in the treatment of clinical conditions associated with the insulin resistance wherein the active ingredient is a compound according to any of claims 1-8.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01066

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 277/34, C07D 263/20, C07D 271/07, A61K 31/425, A61K 31/42, A61K 31/41  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chem.Pharm.Bull., Volume 30, No 10, 1982, Takashi Sohda et al, ""Studies on Antidiabetic Agents. II.1) Synthesis of 5-4-(-Methylcyclohexylmethoxybenzyl thiazolidine-2, 4-dione (ADD-3878) and Its Derivatives"" page 3580 - page 3600 --	1-15
A	EP 0008203 A1 (TAKEDA YAKUHHIN KOGYO KABUSHIKI KAISHA), 20 February 1980 (20.02.80) --	1-15
A	EP 0139421 A1 (SANKYO COMPANY LIMITED), 2 May 1985 (02.05.85) --	1-15

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

3 Sept 1998

Date of mailing of the international search report

21-09-1998

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01066

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5223522 A (DAVID A. CLARK ET AL), 29 June 1993 (29.06.93)  -- -----	1-15

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01066

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 14  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Claim 14 relates to a method of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1 (iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

27/07/98

International application No.  
PCT/SE 98/01066

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		IE 58036 B	16/06/93
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		US 4572912 A	25/02/86
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		FI 904414 D	00/00/00
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		US 5061717 A	29/10/91
		US 5120754 A	09/06/92
		WO 8908650 A	21/09/89